Case Report

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# Drug-induced Gingival Overgrowth Related to Sirolimus and Felodipine

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Drug-induced gingival overgrowth (DIGO) is an adverse drug reaction mainly described with three types of commonly prescribed drugs, namely, calcium channel blockers (CCBs) (nifedipine, diltiazem, and verapamil), anti-convulsants (phenytoin), and immunosuppressive agents (cyclosporine). Numerous reports have associated gingival overgrowth with the newer generation of immunosuppressive agents (tacrolimus, sirolimus, and everolimus), and CCBs (amlodipine, felodipine, nicardipine, and manidipine). Especially, patients concomitantly medicated with an immunosuppressive agent and CCB have a higher DIGO chance. Dentists need to be aware of drugs that induce gingival overgrowth, the possibility of DIGO, and risk factors, and also prevent the progression of DIGO by early detection of DIGO, consultation about the drug change, and the maintenance of strict dental hygiene regimes.

**Key Words:** Calcium channel blockers; Gingival overgrowth; Immunosuppressive agents

## INTRODUCTION

Drug-induced gingival overgrowth (DIGO) is a noted side effect of three types of commonly prescribed drugs, namely, calcium channel blockers (CCBs) (nifedipine, diltiazem, and verapamil), anticonvulsants (phenytoin), and immunosuppressive agents (cyclosporine). Among three categories, it has been reported that newer generation of drugs are also induced gingival overgrowth. The drug categories and representative drugs including the newer drugs are listed in Table 1.[1-5]

Ellis et al.[6] discussed the overall prevalence of gingival overgrowth related to chronic medication with CCBs, addressing it is considerably lower than finding from previous studies. Therefore, the expression of this effect needs cofactors such as the presence of gingival inflammation or concomitant medications inducing gingival overgrowth.

Cyclosporine has become the foundations of immunosuppressive therapy since the early 1980s, and tacrolimus, another calcineurin inhibitor, drastically decreased acute rejection rates since the early 1990s.[7] A contradiction of posttransplantation care is that many of the immunosuppressants, especially calcineurin inhibitors, used to prevent allograft rejection may have serious long-term outcomes on the transplanted tissue and other organ systems such as nephrotoxic, hyperlipidemic, hypertensive, and, to some extent, neurotoxic and hepatotoxic effects.[8] The use of sirolimus, an inhibitor of the mammalian target of rapamycin, seems to reduce the risk for acute rejection and chronic allograft nephropathy.[9]

Gingival overgrowth is another recognized side effect of immunosuppressive therapy. DIGO is characterized by an increase of gingival volume usually in the gingival papillae without extending beyond the mucogingival junction.[10] Because hypertension and nephrotoxicity, adverse effects of cyclosporine, are often treated with CCBs, DIGO is increased under regimens of the combination of cyclosporine and CCB. Cota et al.[11] discussed that the prevalence and severity

**Table 1.** Drug-induced gingival overgrowth-inducing drugs

| Drug category | Anti-convulsants | Immunosuppressive agents | Calcium channel blockers |
|---|---|---|---|
| Drugs | Phenytoin<br>Carbamazepine<br>Valproic acid<br>Phenobarbitone<br>Vigabatrin | Cyclosporine<br>Azathioprine<br>Mycophenolate mofetil<br>Tacrolimus<br>Sirolimus<br>Everolimus | Amlodipine<br>Nifedipine<br>Felodipine<br>Nitrendipine<br>Verapamil<br>Diltiazem<br>Nicardipine<br>Nisoldipine<br>Oxodipine |

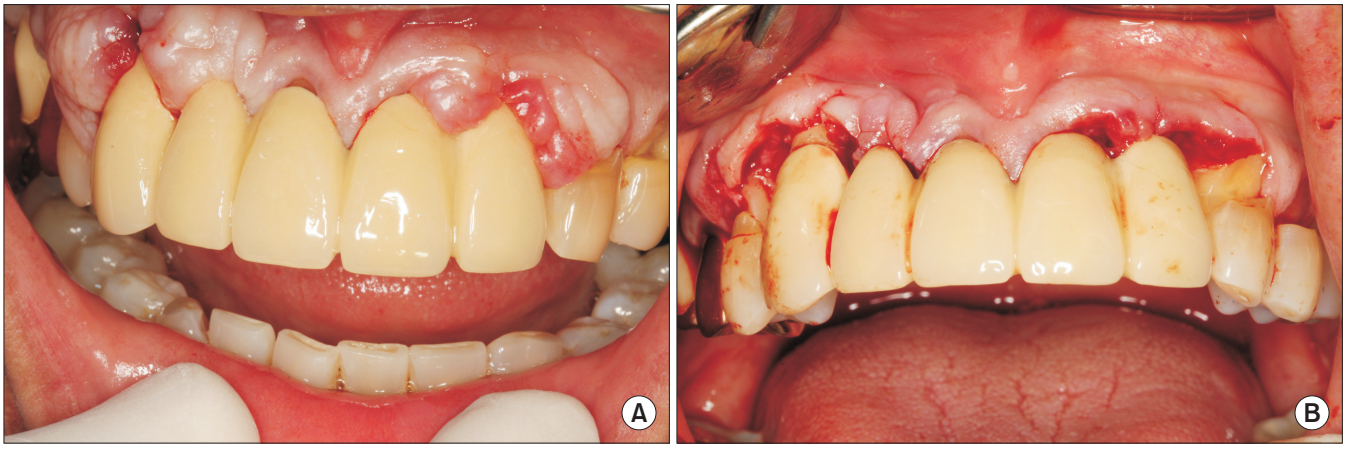


**Fig. 1.** Generalized gingival overgrowth before gingivectomy procedure (A) and after gingivectomy procedure (B) about 4 years prior to first visit.

of gingival overgrowth are higher within immunosuppressive regimens based on cyclosporine compared with tacrolimus and sirolimus, and higher within immunosuppressive regimens based to tacrolimus compared with sirolimus. Although the gingival overgrowth under sirolimus-based immunosuppressive regimens is not clinically significant, it was strongly associated with the concomitant CCB use and the interaction between time since transplant and previous calcineurin use.

This report reviews a case of a 50-year-old man with DIGO related to immunosuppressants and CCBs.

## CASE REPORT

A 50-year-old male presented with generalized gingival overgrowth in the keratinized gingiva which developed 4.5 years prior to his first visit to the clinic. His chief complaint was swollen feeling on the lower left posterior gingiva, and the lower left first and second molar showed no abnormality during clinical examination in the Department of Conservative Dentistry.

The patient had a history of kidney transplant and had been taking with cyclosporine for about 3.5 years. Cyclosporine was changed to sirolimus about 6 years ago. Furthermore, the patient had been taking felodipine for the treatment of hypertension for 9.5 years.

Gingivectomy on the upper anterior gingiva was performed in the Department of Periodontology about 4 years prior to his first visit (Fig. 1), and the gingival overgrowth relapsed. At first visit, clinical examination revealed gingival overgrowth and inflammation on the lower left second molar (Fig. 2) and the upper and lower anterior gingiva (Fig. 3). Generalized alveolar bone loss was observed on the panoramic radiograph (Fig. 4). After oral hygiene instruction was given and chlorhexidine gargle was prescribed to reduce the gingival inflammation, he was sent to periodontist for supportive periodontal therapy.

Scaling and minocycline application were done. Two

months after first visit, gingival inflammation was reduced, but gingival overgrowth persisted (Fig. 5).

## DISCUSSION

Gingival overgrowth has been associated with the administration of immunosuppressant, anticonvulsant, and CCB. A unifying hypothesis of these drugs side effect has been constructed which included the following: 1) bacterial inflammation increasing connective tissue production, 2) inducing drugs causation of fibroblast proliferation and/or increased production of connective tissue, and 3) decreased cellular folate uptake within gingival fibroblasts by possible inhibitory effects upon cation channels.[1)]

The treatment options for DIGO should be based on the medication being used and the clinical presentation of each particular case. Firstly, treatment choices of DIGO that should be decided with the patient's physician include discontinuing or replacing the gingival overgrowth-inducing drugs before gingival overgrowth aggravated. Gingivectomy is needed in advanced gingival overgrowth. Alternative medications to cyclosporine include tacrolimus or sirolimus that has much lower prevalence of gingival overgrowth than cyclosporine. Previous studies showed that prevalence of gingival overgrowth was 60.0%-61.0% for cyclosporine, 26.5%-28.9% for tacrolimus, and 15.6%-20.8% for sirolimus groups in renal transplant recipients, though pharmacological and periodontal variables should be considered in different immunosuppressive regimens.[4,11,12)] Within the group under sirolimus-based immunosuppressive regimens, gingival overgrowth was associated with previous use of cyclosporine and concomitant CCB use.[11)] This interaction may reflect the longer exposure to cyclosporine in previous immunosuppressive regimens and may indicate that gingival alterations are a residual effect of past cyclosporine

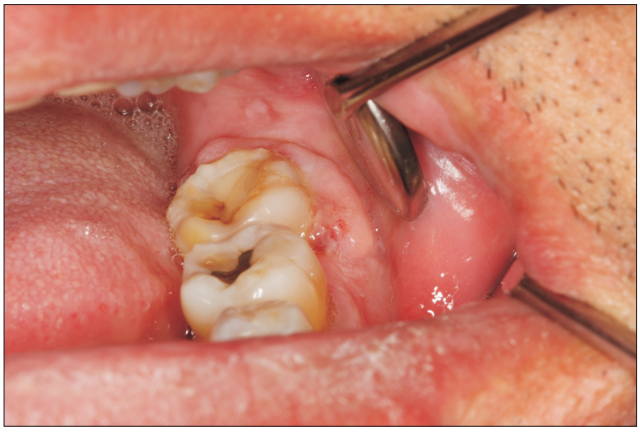

**Fig. 2.** Gingival overgrowth and inflammation on the lower left second molar.

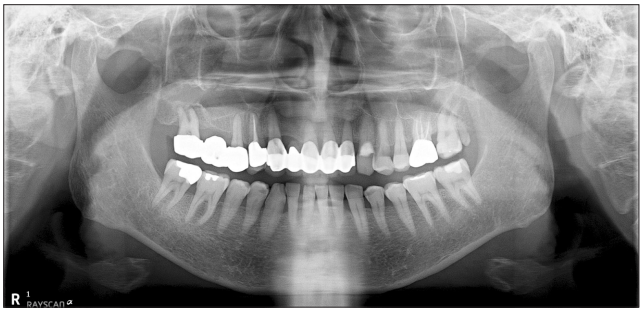

**Fig. 4.** Panoramic radiograph.

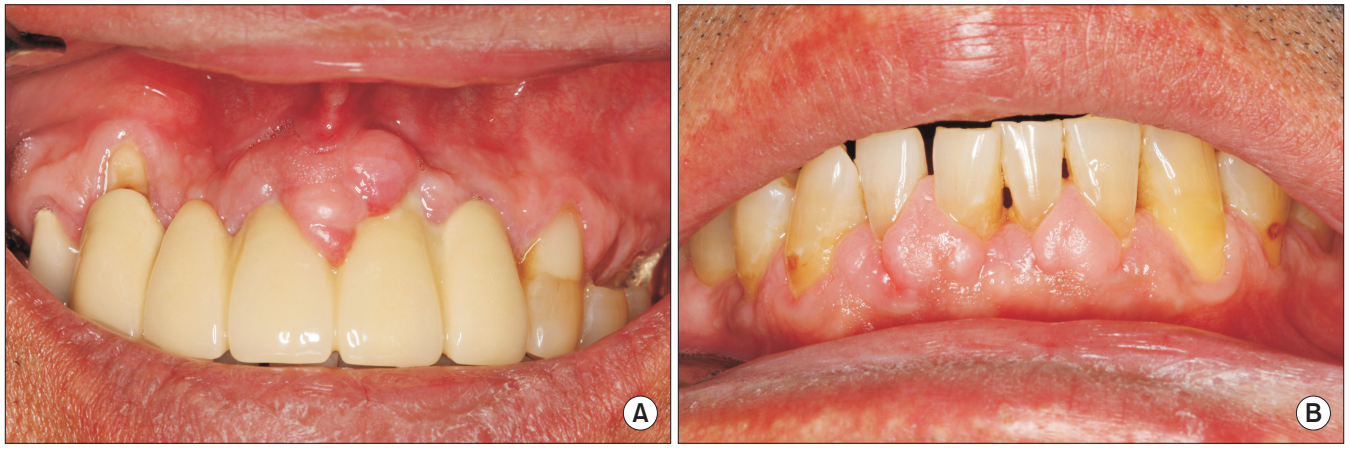


**Fig. 3.** Gingival overgrowth on the upper (A) and the lower (B) anterior teeth at first visit.

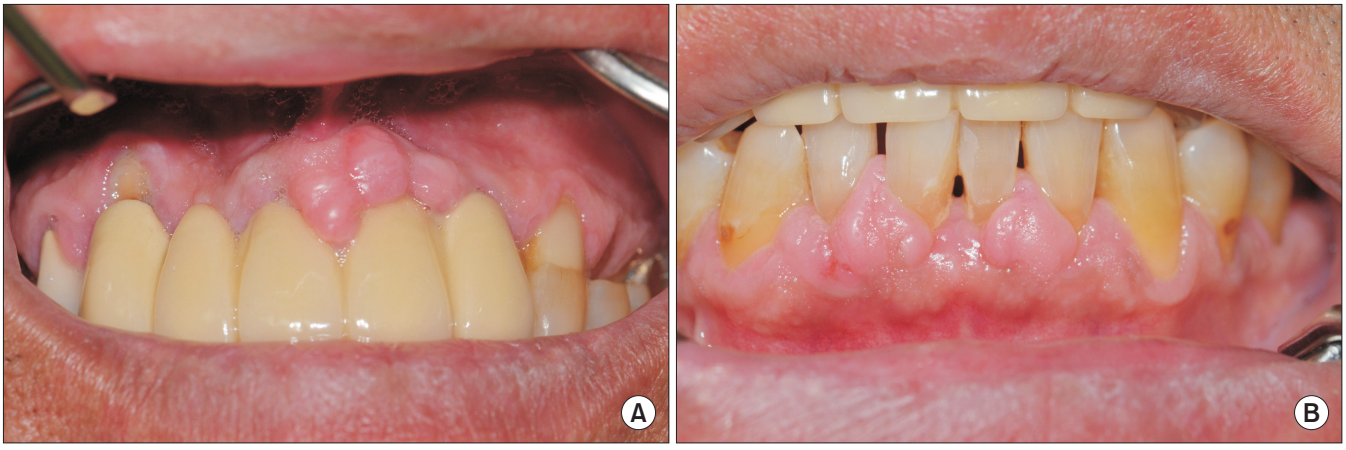


**Fig. 5.** Gingival overgrowth on the upper (A) and the lower (B) anterior teeth at second visit.

exposure. It seems to be impossible to stop or alter immunosuppressant regimen in this case. Therefore, consultation to his physician should be needed to consider whether a different CCB can be substituted for felodipine, or more favorably substitution can be made by a structurally different antihypertensive drug.

The clinician should also emphasize oral hygiene as the first step in the treatment of DIGO, because good oral hygiene and adequate plaque control decreases the degree of the DIGO and improves overall gingival health. Also, frequent supportive periodontal therapy may help in preventing or retarding the recurrence of DIGO in surgically treated cases.[13] Furthermore, adjunctive use of chlorhexidine has been found to be beneficial in decreasing the severity of DIGO.[14] Antibiotics can also be used, and in resistant cases a surgical therapy such as gingivectomy or periodontal flap may be performed, although the condition tends to recur.[13] Alternative treatment options may include folic acid supplementation. According to the unifying hypothesis, DIGO may be secondary to a localized folic acid deficiency. There is evidence that topical administration of folic acid may be efficacious to decrease the incidence and severity of DIGO.[15]

Gingival overgrowth-inducing drugs among immunosuppressant, anticonvulsant, and CCB categories are being updated. It is important to be aware of these newer drugs and relationship between the drugs under concomitant or previous medications.

Findings point to the importance of comprehensive treatment and cooperation between dentists and physicians in the maintenance of the patients under these regimens. Clinicians should first consider the nonsurgical therapy, including the removal of local factors and substitution of the offending drug. If the nonsurgical approach is not effective, periodontal surgery can effectively reduce the DIGO.

Dentists need to be aware of drugs that induce gingival overgrowth, the possibility of DIGO, and risk factors, and also prevent the progression of DIGO by early detection, consultation about the drug change, and the maintenance of strict dental hygiene regimes.

## CONFLICT OF INTEREST

No potential conflict of interest relevant to this article was reported.

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