

Drug Induced Generalized Gingival Enlargement Associated with Alveolar Bone Loss - Case Report

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Abstract

The main purpose of this report is to present a case of gingival enlargement induced by Nifedipin in a Kosovar patient. Several studies has implicated gingival enlargement as a consequence of the administration of Nifedipine. A 62-year-old male hypertensive, under Nifedipin therapy for four years, was referred to the Department of Periodontology and Oral Medicine in University Dentistry Clinical Center of Kosovo. Periodontal clinical examination revealed generalized gingival overgrowth. His periodontal treatment included scaling and root planning and instructions on appropriate method for brushing teeth, antiseptic mouth wash with Chlorhexidin gluconate 0.2%. Patient's hypertensive therapy was replaced by cardiologist with Hydrochlorothiazide 12.5 mg/2 tablet daily and Lerkanidipin-Hidrohlorida 10 mg, 1 tablet daily. Eight months after cessation of the drug Nifedipine and substitution with another class of antihypertensive medication, continuing with nonsurgical periodontal therapy the gingival enlargement dismissed.

It is possible to treat gingival enlargement induced by Nifedipin non-surgically with change of initial antihypertensive therapy, thorough periodontal treatment and accurate oral hygiene. There was significant reduction in the hyperplastic gingiva within 8 months of treatment, without surgical periodontal treatment.

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Introduction

Drug-induced gingival overgrowth (DIGO), referred as drug induced gingival enlargement is a side effect of administration of calcineurin inhibitors such as cyclosporine, anti-convulsing drug such as phenytoin and calcium blocking agents such as Amlodipine and Nifedipine. Hypertension is a progressive disease that affects more than 1 billion people around the world¹. It is a significant contributor to cardiovascular events, cardiac death and kidney disease and uncontrolled hypertension can lead to acute illness such as myocardial infarction and stroke^{2,3}.

Calcium channel blockers are a class of medications that exert effects predominantly in voltage -gated Ca²⁺ channels, located in the plasma membrane which are antihypertensive, anti-arrhythmic and anti-angina drugs. Calcium channel blockers such as Dihydropyridine have been confirmed to be appropriate as a key therapy in patients with hypertension, particularly in those with left ventricular hypertrophy, asymptomatic atherosclerosis, angina pectoris, permanent atrial fibrillation, peripheral artery disease, isolated systolic hypertension, metabolic syndrome and during pregnancy⁴⁻⁶.

Incidence of adverse events reported in clinical trials as a common adverse events of extended-release of Nifedipine mentioned in the literature are: peripheral edema, constipation, arthralgia, back pain, headache, dizziness, nausea, vomiting, increased alkaline phosphatases, fatigue, polyuria, rash erythematous, flushing, palpitation, pruritus⁷⁻¹⁰. Among calcium antagonists, Nifedipine is the drug most commonly related to DIGO, whose prevalence ranges from 20% to 83%¹¹⁻¹³.

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Gingival enlargement (GE) associated with Nifedipine therapy was first reported in 1984¹⁴.

One of the hypothesis emphasizes that the biochemical pathway for drug induced gingival enlargement is influenced by bacterial plaque which causes gingival inflammation which increases the accumulation of gingival connective tissue. The calcium blocking agents decrease folate cellular uptake in gingival fibroblast cell¹⁵.

The etiology for GE is not entirely understood. Risk factors associated with both the development and expression of the drug-induced gingival changes include: age, sex, drug variables, concomitant medication, periodontal variables and genetic factors¹⁶.

Increased levels of various cytokines as transforming growth factor- β (TGF β), fibroblast growth factor, platelet-derived growth factor (PDGF), and connective tissue growth factor (CTGF) are elevated in DIGO. These cytokines play an active role in the development of DIGO¹⁷⁻²⁰.

Interaction between nifedipine and gingival fibroblasts, over production of collagen and extracellular ground substance occurs and leads to an increase in the size of the gingiva²¹. The common characteristics of DIGO includes patient variation in the pattern of enlargement (genetic predisposition), predilection for anterior gingiva, onset within 3 months, changes in gingival contour leading to gingival size, change in gingival color, increased gingival exudate, associated with or without bone loss, associated with or without attachment loss or tooth mobility²².

Case Report

A 63-year-old male patient reported at the Department of Periodontology at the University Dentistry Clinical Center of Kosovo, with main complain gingival enlargement and bleeding. Medical history of patient's revealed he suffered from high blood pressure (155/100) and diabetes mellitus type 2. He has been in antihypertensive drug with Nifedipine 10 mg (2 tab daily) for a period of 4 years, while he noticed GE approximately 6 months after starting the therapy. Patient's family medical history presented diabetes mellitus and hypertension, on maternal side.

On patient's clinical examination it was revealed a generalized chronic periodontitis modified by poor oral hygiene and plaque induced GE affecting all teeth. GE present around teeth in both arches, during clinical examination gingiva was red, smooth, shiny and with no pain during palpation but bled easily while probing (Figure 1-3).



Figure 1. Severe gingival enlargement in maxillary and mandibular arch, of the patient associated with Nifedipine medication.



Figure 2. Severe gingival enlargement of palatal gingiva.



Figure 3. Severe gingival enlargement of lingual gingiva.

Moreover, with development of GE patient's oral hygiene, speech, mastication and esthetic difficulties were induced.

Furthermore, the panoramic radiograph showed generalized bone loss (Figure 4).



Figure 4. Orthopantograph showing mild to moderate bone loss around mandibular teeth.

The patient gave written informed consent and the case had been reviewed and approved by Joint Ethics Committee at the University Dentistry Clinical Center of Kosovo.

Patient followed our clinic's protocol, which include complete hematologic examination, leukocytes count, C reactive protein (CRP) and sedimentation rate, which all were in within range, except of Hb-A1c (glycated hemoglobin) levels were 8.80.

Primarily patient was referred for consultation with cardiologist, intended for reviewing the anti-hypertensive therapy protocol. Due to his unstable artery blood pressure, cardiologist did not sign the consent for periodontal surgery, but consent was obtained to continue with the non-surgical periodontal treatment plan.

Therefore, our treatment plan for patient included: termination of the affecting drug and its substitution with another class of antihypertensive medication, in order to prevent recurrence of the lesions.

As a result, patient's cardiologist altered the antihypertensive medications to Co-lrbesartan tablets (Hydrochlorothiazide) 150 mg/12.5 mg, two tablets daily and Lercanil (Lerkanidipin-Hidrohlorida) 10 mg, one tablet daily.

Patient's treatment plan included: initial therapy, antiseptic mouth wash Chlorhexidin gluconate 0.2%, scaling and root planning and

instructions on appropriate method for brushing teeth. In a first 3 months, patient was examined for signs of improvement weekly and afterword's once in only 2 months (Figure 5).



Figure 5. Three months post non-surgical periodontal treatment.



Figure 6. Eight months post non-surgical periodontal treatment.



Figure 7. Eight months post non-surgical periodontal treatment of lingual gingiva.

In patients 8 months' follow-up period, patient was recalled at regular intervals for control, and there was a marked reduction in the gingival enlargement (Figure 6-8).



Figure 8. Eight months post non-surgical periodontal treatment of palatal gingiva.

Discussion

The clinical periodontal treatment of the GE consists of periodic prophylaxis, scaling, root planning and periodontal surgery²³.

Literature shows that nifedipine-induced gingival enlargement may be reduced or prevented by good plaque control, aimed at reducing gingival inflammation²⁴.

Tavassoli et al., reported a higher incidence of GE in patients using nifedipine for more than 4 years²⁵.

The identification of risk factors associated with prevalence and severity of drug-induced gingival overgrowth is very important. The studies provide evidence that infection with a periodontal pathogen *Porphyromonas gingivalis* may play a role in the pathogenesis of central nervous system in rabbit²⁶. Gingival enlargement can be caused by local and systemic factors²⁷, alveolar bone loss showed bilateral or symmetrical pattern and percentages of vertical bone defect were found higher at the mesial of maxillary second molar²⁸. Severity of GE is well correlated with poor oral hygiene²⁹.

Considering that hypertensive drugs, respectively Nifedipine is usually prescribed to middle aged and older patients, until today age has not been acknowledged as a risk factor for GE³⁰.

On the other hand, studies in animals and humans recommend that sex might have an influence in the drug induced GE, where females are less predisposed compare to men³¹.

Various studies suggest that a daily dose of 5mg or higher of Amlodipine, in some patients could act as a risk factor for gingival overgrowth^{32,33}.

However, the gingival enlargement is usually noted within one to two months after the initiation of nifedipine therapy and appears to primarily affect interdental papilla and labial gingiva³⁴. Ellis et al. underscored that plaque index and bleeding index on probing were strongly correlated with the severity of gingival overgrowth in patients using Nifedipine³⁵.

Conclusions

Gingival enlargement is an often side effect of Nifedipine's and it is a frequent oral finding in these group of patients. Until now, many physicians and/or cardiologists are unaware of the relationship between Nifedipine and GE, as its side effect, therefore this indicates the importance of interaction between healthcare professionals. Replacement of antihypertensive therapy and combined with non-surgical periodontal treatment, are vital step in management of drug induced gingival enlargement.

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Declaration of Interest

The authors declare that there is no conflict of interests regarding the publication of this paper.

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