

NONSURGICAL MANAGEMENT OF AMLODIPINE INDUCED GINGIVAL ENLARGEMENT: A CASE REPORT

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ABSTRACT:

Antihypertensive drugs in the calcium channel blocker group are extensively used in elderly patients. Gingival enlargement associated with Nifedipine was first reported in 1980's and is very rarely reported to be associated with Amlodipine and Felodipine. The mechanism through which these medications trigger a connective tissue response are still poorly understood. The most effective treatment of drug induced gingival overgrowth is withdrawal or substitution of medication combined with meticulous oral hygiene, plaque control, and removal of local irritants. When these measures fail to resolve the enlargement, surgical intervention is recommended. This case reports a rare case of Amlodipine induced gingival enlargement. The patient was successfully managed by drug substitution and nonsurgical periodontal therapy.

Key words: Nonsurgical therapy, Amlodipine, Calcium channel blocker, drug induced gingival enlargement.



INTRODUCTION:

Gingival overgrowth is a fibrotic enlargement of the gingiva that can be induced by various pharmacologic agents through poorly understood mechanisms. Proliferative overgrowth of the gingiva makes it more difficult for patients to maintain oral hygiene. Changes in the gingiva can range from minor to complete

coverage of the teeth. Such changes are unsightly and may result in pain, difficulty in eating, and an undesirable breath odor.^[1] Mechanical obstruction could prevent the eruption of developing teeth.^[2] There is a potential for candida overgrowth in patients who are being treated with immunosuppressants.^[3]

The three classes of drugs associated with gingival overgrowth are

- Antiepileptics (especially phenytoin [Dilantin]),
- Immunosuppressant-cyclosporin,^[4] and
- calcium antagonists.^[5] –
 - Dihydropyridines (including Nifedipine,^[6] Felodipine,^[7] Nitrendipine,^[5] and Amlodipine^[8]) and
 - Nondihydropyridines Diltiazem,^[9] and Verapamil, have been linked to gingival overgrowth.

Although pharmacologic effect of each of these drugs is different and directed toward various primary target tissues, all of them seem to act similarly on secondary target tissue, i.e., the gingival connective tissue, mainly fibroblast, causing common clinical histopathological findings.

Calcium channel blockers are widely used in medical practice for the management of cardiovascular disorders. Gingival overgrowth is now a recognized unwanted side effect associated with many of calcium channel blockers. Of this large group of drugs, the dihydropyridines are the agents most frequently implicated. Amlodipine, a newer agent of dihydropyridine, used for treatment of hypertension and angina, was first reported for causing gingival overgrowth as side effect, by Seymour et al in 1994.^[8]

Pharmacokinetics: Calcium channel blockers act by inhibiting calcium ion influx across the cell membrane of cardiac and smooth muscle cells, thereby interfering or blocking mobilization of calcium intracellularly^[10]. Depending on the specific agent, this results in dilatation of coronary arteries and arterioles, as well as decreased myocardial contractility and oxygen demand. Since 1978, the substituted dihydropyridines have been used to treat angina pectoris, postmyocardial syndrome and hypertension^[11]. The primary undesirable side effect of the calcium channel blockers results from excessive vasodilatation, which manifests as facial flushing, dizziness, headache and edema. Ramon et al.^[12] published the first report in the scientific literature that associated a calcium channel blocker (nifedipine) with the occurrence of gingival overgrowth in 1984. Since that time, human case reports of this associated side effect have been related to five other agents in this class, including amlodipine, felodipine, diltiazem, nitrendipine and verapamil. Another agent in this group, oxodipine, has been associated with gingival overgrowth in dogs.

Dihydropyridines: Gingival overgrowth has been reported in 15% to 83% (composite average=42.5%) of patients taking nifedipine approximately 21% of patients taking diltiazem and about 4% of those medicated with verapamil.^[13] In a recent study, Nery et al.^[14] reported a 43.6% prevalence of gingival hyperplasia among 181 patients taking nifedipine as compared with 4.2% in 71 control patients

who were not taking phenytoin, calcium channel blockers or cyclosporin. Ishida et al. [15] and Nishikawa et al. [16] reported that a minimum blood level of 800 ng/ml of nifedipine resulted in gingival overgrowth in a rat model and that the degree of overgrowth depended on increased concentrations above this threshold value. Human studies have not supported a relationship between dose or plasma levels of these agents and gingival overgrowth. The authors suggest that the very high concentrations of nifedipine that may occur in gingival crevicular fluid favor the likelihood of toxic effects. [17]

As previously noted, several other substituted dihydropyridine calcium channel blockers are available that exert slightly different cardiovascular effects based primarily on selected sites of action.

Amlodipine is an anti-anginal calcium channel blocker that acts by decreasing myocardial contractility and oxygen demand and that dilates coronary arteries and arterioles. In a report of three cases of associated gingival overgrowth, Seymour et al. 1994 detected amlodipine in the gingival crevicular fluid of each individual, all of whom were long-term recipients of the medication.

In 1990, Brown et al. reported the first case of gingival overgrowth induced by nitrendipine. At that time, this agent was being used in an experimental protocol to treat hypertension and congestive heart failure.

Lombardi et al. reported gingival overgrowth in a patient taking felodipine, a calcium channel blocker that selectively inhibits smooth muscle without directly causing negative cardiac effects and that has proven effective in managing hypertension.

The role of drugs in the pathogenesis of gingival overgrowth:

Fujii et al. in 1994 tested the effect of calcium channel blockers on cell proliferation, DNA synthesis and collagen synthesis on gingival fibroblasts from human nifedipine responders and non-responders. Cells were tested with nifedipine, diltiazem, verapamil and nicardipine in vitro. Responder fibroblasts trended toward greater cellular proliferation rates, DNA synthesis and collagen synthesis compared to the cells from nonresponders or phenytoin positive controls. Barclay et al in 1992 notes that the collagenolytic effects of inflammatory cells and synthesis of collagenase are calcium-dependent cellular events. Nifedipine, phenytoin and cyclosporin A may interfere with calcium transport and calcium-dependent processes. These agents may reduce cytosolic calcium levels in gingival fibroblasts and T cells, thus interfering with Tcell proliferation or activation and collagen synthesis by gingival fibroblasts. Lucas et al. [18] and Jones et al. suggested that gingival overgrowth results from overproduction of extracellular ground substance characterized by increased presence of sulphated-mucopolysaccharides (glycosaminoglycan) and collagen, and abundant active fibroblasts. McKeivitt et

al. in 1995 used fibroblasts from responders and non-responders to study the effect of phenotypic differences in growth, matrix synthesis and response to nifedipine. The responder cells presented increased growth potential and produced greater levels of protein and collagen than did non-responder cells.

Histological characteristics: Although the connective tissue changes may be predominant, the epithelium exhibits parakeratosis, proliferation and elongation of the rete ridges, which extend some distance into the lamina propria. Van der Wall *et al.* in 1985 reported a ten-fold increase in epithelial width (normally 0.3 to 0.5 mm), inflammatory changes accompanied by edema, and infiltrates of lymphocytes and plasma cells. In a study of 34 biopsies of nifedipine gingival overgrowth, Barak *et al.* in 1987 described thickening of the spinous cell layer, slight to moderate hyperkeratosis, fibroblastic proliferation and fibrosis of the lamina propria. These changes were accompanied by increased capillary vascularity and slight perivascular inflammation.

Clinical Features: Clinical manifestation of gingival enlargement frequently appears within 1 to 3 months after initiation of treatment with the associated medication. Gingival overgrowth normally begins at the interdental papillae and is more frequently found in the anterior segment of the labial surfaces. Gradually, gingival lobulations are formed that may appear inflamed or more fibrotic in nature, depending on the degree of local

factors induced inflammation. The fibrotic enlargement normally is confined to the attached gingiva but may extend coronally and interfere with esthetics, mastication, or speech. Disfiguring gingival overgrowth triggered by this medication is not only aesthetically displeasing but often impairs function and access for oral hygiene, resulting in an increased susceptibility to oral infection, caries, and periodontal diseases.

Prevention and treatment of gingival enlargement: Control of gingival inflammation and maintenance of effective oral hygiene are key factors in preventing and managing gingival overgrowth associated with this class of medications^[19]. The basic approaches to therapy closely parallel to those for anticonvulsants and cyclosporine-associated gingival enlargement. A 3-month interval for periodontal maintenance therapy has been recommended for patients taking drugs associated with gingival enlargement.^[20] Each recall appointment should include detailed oral hygiene instruction and complete periodontal prophylaxis, with supra-gingival and sub-gingival calculus removal as needed. In some instance orthodontic bands and/or appliances should be removed.

Treatment:

Drug Substitution/withdrawal: The most effective treatment of drug-related gingival enlargement is withdrawal or substitution of medication. Unfortunately, not all patients respond to this mode of treatment especially those with long

standing gingival lesions. Patients must be informed of the tendency for the gingival enlargement to recur as long as the associated medication is continued. In instances where alternate medications can be used, cessation of the associated agent has been shown to result in tissue reduction [21]. Regression of nifedipine-induced gingival overgrowth has been reported following a change in medication to isradipine, a companion dihydropyridine calcium channel blocker. Although discontinuing the use of nifedipine has resulted in gingival improvement within 1 week, appreciable response may require much longer time. Reinstitution of nifedipine therapy following withdrawal has resulted in recurrence of the gingival overgrowth within 4 weeks [22].

Non-Surgical treatment: Professional debridement with scaling and root planning as needed has been shown to offer some relief in gingival overgrowth patients. Hancock & Swan (20) successfully achieved significant reduction of nifedipine-induced gingival overgrowth by thorough scaling and root planing and meticulous plaque control.

Surgical Periodontal treatment: Because the anterior labial gingiva is frequently involved, surgery is commonly performed for esthetic reasons before any functional consequences are present. The classical surgical approach has been the external bevel gingivectomy. However a total or partial internal gingivectomy approach has been suggested as an alternative. This more technically demanding approach has

the benefit of limiting the large denuded connective tissue wound that result from the external gingivectomy, thereby minimizing postoperative pain and bleeding.

The use of carbon dioxide lasers has shown some utility for reducing gingival enlargement, an approach which provides rapid post operative hemostasis. Consultation with the patient's physician prior to surgical treatment regarding antibiotic and steroid coverage should take place in the immunosuppressed patient.

CASE DETAIL:

A 60 year female patient visited to the dept. of periodontics of Rama dental college, hospital & research centre, Kanpur, with the chief complain of bead like enlargement, bleeding and painful gum since a month.

The bead like enlargement appeared first in the interdental papilla of maxillary and mandibular anterior teeth and gradually involves the facial and lingual aspect. Enlargement slowly increased in size and spread to the posterior areas. Patient also complained of bleeding from the gingiva while brushing, soreness and deep gnawing pain.

Her Medical history revealed that she was hypertensive, and on Amlodipine (5mg twice daily) therapy since a year. Patient was not suffering from any other illness/drug allergy and she was not taking any other kind of medication.

On Intra-oral examination, generalized gingival enlargement with increased severity in maxillary arch and mandibular anterior region was note. Oral hygiene maintenance was poor. The enlarged gingiva was erythematous , soft and edematous, and showed a lobulated surface with absence of stippling. There was generalized bleeding on probing. Heavy presence of calculus was also noted. Periodontal examination revealed generalized moderately deep pocket. 31 and 41 were grade III mobile (according to miller’s classification of mobility, 1950) ^[20] with severe bone loss and were indicated for extraction. No significant Radiographic changes were observed except for a moderate generalized bone loss.

Initial visit:



Figure 1: Buccal view



Figure 2: Palatal and lingual view

The case was diagnosed as generalized chronic periodontitis with drug induced gingival enlargement (Combined enlargement – *Inflammatory and Amlodipine induced*). Probing depth was more than 6 mm irt 11,12,13,14,15,21,22,23,24,25,32,33,43 and 44. Request was sent to physician for the drug substitution and consent was taken for the planned periodontal treatment. *Amlodipine was substituted with Losartan potassium and chlorothiazide combination (50 mg, 12.5 mg once daily)*. Since the patient was not willing for extraction of 31, and 41 phase I therapy was initiated. Scaling & root planning was performed under local anesthesia. Oral hygiene instructions were reinforced and were prescribed 0.2% chlorohexidine mouthwash twice daily and patient was recalled after 15 days.

15 days after therapy:



Figure 3: Buccal view



Figure 4: Palatal and lingual view

On examination at the first follow up after nonsurgical periodontal therapy, patient had relief from soreness and painful gums. Intra-oral examination revealed slight improvement in the condition of gingiva. The Intensity of erythema and

bleeding on probing had subsided marginally. The degree of gingival enlargement was slightly reduced. Root planning was repeated and oral hygiene instructions were reinforced. Patient was recalled after 21 days, but patient, failed to follow the appointment, and she returned after a gap of 4 months.



Figure 5: Buccal view



Figure 6: Palatal and lingual view

Four months after phase I therapy:

On examination, oral hygiene maintenance was good and complete resolution of gingival enlargement was noted. Pocket depth in 11, 12, 13, 14, 21, 22, 23, 24 had reduced. 13 showed a persistent mild gingival enlargement. Full mouth scaling and root planning was performed and curettage was repeated in 13.

CONCLUSION:

The reported case is an example of generalized chronic periodontitis. This was superimposed by a combined type of gingival enlargement; basically a drug induced one, complicated by inflammatory changes due to plaque accumulation. Moreover, hormonal changes due to menopause appear to

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contribute further to the enlargement of gingival tissues. The use of medications with the potential to contribute to the development of gingival overgrowth is likely increase in the years to come. Among the old and relatively new pharmacologic agents involved in gingival enlargement, overall, phenytoin still has the highest prevalence rate (approximately 50%), with calcium channel blockers and cyclosporine associated enlargements about half as prevalent. Current studies on the pathogenesis mechanism of drug associated enlargement are focusing on the direct and indirect effects of these drugs on gingival fibroblast metabolism. If possible, treatment is generally targeted on drug substitution and effective control of local inflammatory factors such as plaque and calculus. When these measures fail to cause resolution of the enlargement, surgical intervention is recommended. These treatment modalities, although effective, do not necessarily prevent recurrence of the lesions. Newer molecular approaches are needed to clearly establish the pathogenesis of gingival overgrowth and to provide novel information for the design of future preventative and therapeutic modalities.

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