

AMLODIPINE INDUCED GINGIVAL OVERGROWTH- A RARE CASE REPORT

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ABSTRACT

Amlodipine, a third generation calcium channel blocker, is a comparatively new and safe drug which is being routinely and vastly prescribed for the management of cardiovascular disorders. It is of concern and challenge for the Periodontists, because it has been found to cause gingival over growth leading to unaesthetic appearance and formation of new niches for periodontopathogenic bacteria. Incidence of promoting gingival overgrowth with Amlodipine is much lower with very few cases reported till date. This case report describes a rare case of Amlodipine induced gingival over growth in hypertensive patient who was under 'Amlosafe-AT' medication, an Amlodipine combination drug and has also shown that periodontal treatment can yield satisfactory clinical response without change in associated drug.

KEYWORDS: Amlodipine; Gingival overgrowth; Antihypertensive

INTRODUCTION

There is an ever increasing number of medications which induce gingival overgrowth, among those medications, the total number of annual prescriptions of Calcium channel blockers (CCB) which are used for angina or peripheral vascular disease in extensively elderly patients has continued to rise in recent years. Among these large groups of drugs, the dihydropyridines are the agents most frequently implicated. The medication induced gingival overgrowths occur as a side effect of drugs used mainly for non dental treatment for which the gingival tissue is not the intended target organ. Amlodipine a newer agent of dihydropyridine is a third

generation of Calcium channel blocker which is shown to have longer action and weaker side effect compared to first generation such as nifedipine. Side effects of amlodipine usage involve headache, dizziness, edema, flushing, palpitation and rarely gingival overgrowth.^[1] Although the pharmacologic effect of those drugs which are associated with gingival overgrowth (Table 1) are different and directed towards various primary target tissues, all of them seem to act similarly on a secondary target tissue i.e. the gingival connective tissue. First reported case of amlodipine associated gingival overgrowth was by Ellis & Seymour *et al.*, in 1994.^[1] Recently, (Lafzi *et al.* 2006)^[2] has reported rapidly developed gingival hyperplasia in patient received 10 mg per day of amlodipine within two months of onset. Prevalence of gingival overgrowth in patients with Amlodipine was reported to be lower than nifedipine rate (Table 2).^[3] Clinically, the enlargement is usually seen 3-6 months following the initiation of the drug in question. The overgrowth of the gums is generally painless and predominantly involves the maxillary and mandibular anterior teeth usually affecting the marginal and inter-dental gingiva. However, gingival enlargements as a side effect of drugs are usually superimposed with an inflammatory condition due to development of unfavorable gingival contours. The enlarged gingival tissues accumulate plaque and also hinder the maintenance of routine oral hygiene which poses a major problem resulting in the destruction of the underlying bone and attachment loss leading to periodontitis. In this case report, treatment of gingival overgrowth in hypertensive patient, who was under medication on Amlodipine- AT was done under the following phases (Table 3).

CASE REPORT

A 45- year old female patient referred to the



Fig. 1: Pre-operative photograph (Labial View)



Fig. 2: Pre-operative photograph (Palatal view)



Fig. 3: Pre-operative photograph. (Lingual view)



Fig. 4: Pre-operative OPG



Fig. 5: Treatment Plan



Fig. 3c: After 2 Month Phase 1 Therapy



Fig. 3d: During Surgery



Fig. 3e: Overgrowth Tissue Removed



Fig. 3d: Suture Placed



Fig. 3e: Vocopack Placed



Fig. 4a: 10 Days Post-operative



Fig. 4b: 4 Month Post-operative

Table 1: Drugs Commonly Associated With Gingival Overgrowth

CATEGORY	DRUGS	BRAND NAMES
Anti-epileptics	Phenytoin	Dillantin, eptoin
	Phenobarbitone	Gardinal, phenetone
	Primidone	Mysoline
	Valproic acid	Valprid, valtec, valprin
Calcium channel blockers Dihydropyridines	Nifedipine	Adalat
	Amlodipine	Amcard, amdepin
	Felodipine	Felogard
	Nitrendipine	Nitrepin
	Verapamil	Nicarpress-r
Phenylalkylamine	Diltiazem	Dilzem
Benzothiazepine	Bepridihydrochloride	Bepricor
Immunosuppressants	Cyclosporine	Cyclophil
Miscellaneous	Erythromycin	Althrocin
	Sertaline	Daxid, setalin

Table 2: Estimated Rates Of DIGO According To Most Frequently Reported Prevalence Rates

Category	Pharmacologic agent	Trade name	Prevalence
Anticonvulsants	Phenytoin	Dilantin	50%
	Sodium valproate	Depakene, depacon	Rare
	Phenobarbitone	Phenobarbital	<5%
	Vigabatrin	Sabril	Rare
	Carbamazepine	Tegretol	None reported
Immunosuppressants	Cyclosporin	Neoral, sandimmune	Adults 25- 30% Children >70%
Calcium channel blockers	Nifedipine	Adalat, nifecard	6-15%
	isradipine	Dynacirc	None reported
	Felodipine	Agon, felodur	Rare
	amlodipine	Lotel, norvasc	Rare
	Verapamil	Calan, covera	<5%
	Diltiazem	Cardizem, dilacor	5-20%

A 45-year old female patient referred to the Department of Periodontology complaining enlarged gums in the upper and lower front teeth region for 1 year and was uncomfortable as the topography of gingiva interfered for routine tooth brushing and chewing food. She also complained of burning sensation occasionally with hot and spicy food. A medical history revealed that the patient was hypertensive for 9 years. Patient was under medication on beta blocker (Atekind 50) for 7 years, later as per physician advice

medication was changed to Amlosafe-AT i.e. Amlodipine 5mg, Atenolol 50mg for 2 years and continues the same once daily. General physical examination revealed moderately built. Patient with normal gait. Intra oral examination revealed, generalized overgrowth of gingiva more in the anterior region and less pronounced at the upper right quadrant (Fig. 1). Grade II, bleeding on probing was detected on all affected areas. Palatal aspect of 22 23 24 revealed soft mass of gingiva with erythematous surface (Fig. 2). Gingival

Table 3: Details Of The Demographics, Medical History And Treatment Of The Clinical Case

SL No.	Age	Sex	Treatment time with amlodipine	Dose of amlodipine	Presence of other disease	Other drugs prescribed	Treatment rendered
1.	45yr	Female	Two year	5mg	Hypertension	Atenolol 50mg	<ul style="list-style-type: none"> • Thorough phase I therapy. • Surgical excision of residual gingival overgrowth by internal bevel gingivectomy and external bevel gingivectomy • Maintenance and supportive therapy.

consistency was firm with respect to 17 16 15 14 13 31 32 41 42 soft and edematous with respect to all other areas. Gingival contour showed lobulated interdental papilla and blunt edge. Facial & lingual gingival margins were united, and was more pronounced with respect to 23 24 25 41 42 (Fig. 3). Gingival recession was with respect to 31 41. Tooth 37 was deeply carious. Presence of very poor oral hygiene with abundant plaque and calculus along with halitosis was noticed. Periodontal pockets were more/equal to 6mm in relation to II & III quadrant. Grade I mobility was noticed with 21 22 42 44 45 and Grade II mobility with 24 25 31 32 41. Furcation involvement was with respect to 36 37. Based on medical history, drug history and clinical examination of the patient, provisional diagnosis of combined gingival enlargement was made i.e. drug (amlodipine) induced gingival enlargement combined with generalized chronic periodontitis. Complete hemogram of the patient was done, but all the parameters were within the normal range. Orthopantomogram was taken which revealed generalized bone loss. (Fig. 4)

TREATMENT

The details of the treatment were explained and an "Informed Consent" was obtained and following protocol was followed (Fig. 5). Phase I therapy: Quadrant wise Scaling and root planing performed followed by Oral hygiene instructions. Root canal treatment was performed with respect to 37. After phase I therapy (2 months) there was a marked reduction in the enlargement with respect to I & IV quadrants. Hence treatment was restricted to non-surgical therapy. Except a moderate amount of residual gingival pockets

(4mm) in relation to 41 42 43 was present (Fig. 6) and residual gingival enlargement and periodontal pockets (6mm) were observed with respect to II & III quadrants which required surgical therapy. Phase II therapy (surgical phase): Technique followed was External bevel gingivectomy with respect to 41 42. Internal bevel gingivectomy with respect to II & III quadrants under local anesthesia using 2% lignocaine hydrochloride with adrenaline 1:80,000 solution. For Internal bevel gingivectomy, incision was placed and flap elevated, triangular wedge of tissue created by three incisions is removed along with gingival mass from palatal aspect and sharp, thin flap margin was obtained (Fig. 7). During surgery, tissue sample excised from palatal aspect with respect to 22 23 24 & with respect to 31 32 33 was stored in formalin and subjected to histopathological study. Hemostasis was achieved with interrupted sutures. Periodontal dressing (Vocopack) was placed along with post surgical instructions (Fig. 8). Analgesics were prescribed and patient was recalled for review after 10 days (Fig. 9). Histopathological examination revealed parakeratinized stratified squamous epithelium which is atrophic in few areas and hyper plastic in other areas with thin long rete pegs extending into the connective tissue. The underlying connective tissue is highly collagenous with wavy bundles of collagen fibers. Focal collection of inflammatory cells and blood vessels can be seen. Finally correlating with the clinical history & the histological picture, it was diagnosed as Amlodipine induced fibrotic gingival overgrowth. After 10 days, adequate healing and improved esthetic appearance was observed along with

good home care oral rinse of 0.2% chlorhexidine twice daily. Patient under review from past 6 months and no sign of recurrence has been observed (Fig. 10).

DISCUSSION

Presently the preferred terminology for gingival hyperplasia/hypertrophy is gingival overgrowth (GO). Seymour *et al.*, (1996)^[4] gave a review on the pathogenesis of drug-induced gingival overgrowth in which they considered it as a multi factorial model. Several factors like age, genetic predisposition, pharmacokinetic variables, alterations in gingival connective tissue homeostasis, histopathology, ultrastructural factors, inflammatory changes and drug action on growth factors may influence the relationship between the drugs and gingival tissues. The exact mechanism of CCB's and the increased risk of gingival overgrowth is not completely understood. GO is a calcium dependent process. CCB's inhibit the intercellular uptake of calcium & this inhibitory action may affect the secretory properties of gingival fibroblasts or the production of collagenases. This may result in over stimulated gingival fibroblasts and cause increased deposition of extracellular matrix components, such as glycosaminoglycans. Amlodipine is more polar than the other dihydropyridines, with a pka value of 8.7. Thus, the drug may not pass through cell membranes without an active transport mechanism. By contrast, nifedipine is intensely lipophilic and will dissolve readily within the cell membrane & pass into the cytoplasm. The majority of amlodipine will be tissue bound (& hence "inactive") rather than circulating freely in blood. Not all the patients receiving the same drug develop gingival overgrowth; possible reason can be that individuals with gingival overgrowth have fibroblasts with an abnormal susceptibility to the drug. It has been proposed that the susceptibility to pharmacologically induced gingival enlargement may be governed by existence of differential proportions of fibroblast subset in each individual which exhibit a fibrogenic response to these medications.^[5] It has also been shown that the functional heterogeneity exists in gingival fibroblasts in response to various stimuli.^[6] Interleukin-6 plays a role in fibrogenic responses of gingiva to these medications and results in fibrotic gingival enlargement.^[4]

Interestingly in this case report, patient was on beta blocker & then combined with amlodipine. The role of beta blocker in causing gingival overgrowth cannot be ascertained. Study by Mishra P & Pradhan S (2009)^[7] showed the prevalence of gingival enlargement was higher in patients CCBs (71.1%) followed by ACE inhibitor (21.5%) and β -blockers (7.4%) & concluded that patients on antihypertensive agents are at increased risk for gingival enlargement and inflammation is an important cofactor for the expression of this effect. Drug-induced gingival overgrowth usually occurs within the first 3 months of starting drug therapy at a dose of 10mg/day, the present case is interesting as it occurred with a low dose of amlodipine 5mg/ day and appeared on administration for 7 months. Recently Chaturvedi R and Jain A (2011)^[8] in their case series, showed that patient on even 2.5mg of amlodipine and atenolol 25mg once daily resulted in a significant gingival overgrowth. The reported case was superimposed by a combined type of gingival enlargement with generalized chronic periodontitis. This is basically a drug induced one, complicated by inflammatory changes due to plaque accumulation. The nature of the relationship between plaque and the expression of gingival overgrowth is unclear. This case showed a marked reduction of overgrowth in upper right and lower quadrant following scaling and root planing. This goes in accordance with the findings of Hancock R H 1992.^[9] The prevalence and severity of the lesions are greater in patients taking cyclosporine and a calcium channel blocker simultaneously. This case report also demonstrated that without a change in associated drug, periodontal treatment alone can yield satisfactory clinical response (Ikawa *et al.* 2002).^[10] However there is possibility for recurrence as long as the associated medication is continued and other risk factors persist. Therefore patient must be informed of this tendency and the importance of effective oral hygiene as key factors in preventing and managing GO associated with these drugs.

CONCLUSION

The use of medications with the potential to contribute to the development of GO is likely to increase in the years to come and physicians may be very reluctant to modify an effective drug

regime 'just for gums', thus, dental professionals needs to emphasis on this issue, to the various medicine experts to minimize the prescriptions. Physicians and dentists should be aware of the etiologic medications that can induce gingival overgrowth and be able to identify changes in the oral cavity in such patients and to prevent, diagnose, and successfully manage them. Unfortunately most physicians fail to appreciate oral biology and oral pathology. Thus cooperative teamwork between the patient, his physician, and the dental health care professional is mandatory. Various treatment modalities available, 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 preventive and therapeutic modalities.

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