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Amlodipine induced gingival enlargement - presentation of a clinical case series.

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Abstract

Objectives: Gingival enlargement as an adverse effects of drugs has been found to be long associated with the use of anticonvulsants; phenytoin, anti-hypertensives; calcium channel blockers and immunosuppressants; cyclosporine. Nifedepine was found to cause gingival overgrowth with an incidence ranging from 15-85%. However, Amlodipine a relatively newer agent of the same group which is being routinely and vastly prescribed either alone or as part of combination therapy to middle to older aged adults has also been found to exhibit this adverse effect with very few cases reported till date. The effect of the dose of amlodipine on the severity of gingival enlargement needs to be assessed.

Study design: A clinical presentation of a series of five cases in the age range of 45-65 yrs with gingival over-growth as a side effect of therapy with amlodipine is presented with prescription of variable doses of 2.5 mg, 5 mg and 10 mg per day. A brief review on the pathogenesis of this condition, commonly associated etiological mechanisms and sequence of periodontal therapy rendered have also been included.

Conclusion: Irrespective of the dose of amlodipine administered, gingival enlargement continues to be a predominant side effect in all of the five cases presented. The accentuated gingival contours accumulate plaque leading further to the destruction of the underlying periodontium. Dental professionals need to identify and then guide the patient to seek necessary medical intervention.

Key words: Amlodipine, hypertension, gingival enlargement, anti-hypertensives, internal bevel gingivectomy.

Introduction

Gingival enlargements are commonly seen as a side effect of various groups of medications which includes: Anticonvulsants, anti-hypertensives; esp. Calcium channel blockers and immunosuppressants. Amlodipine is a third generation dihydropyridine which has been found to be very useful in middle aged to older aged adult patients for various cardiovascular conditions. It functions by inhibiting calcium ion influx across cell membranes of heart and smooth muscles thereby, blocking its intra-cellular mobilization (1). The incidence of gingival enlargement with amlodipine was reported to be much lesser than nifedipine (2,3), however; recently large numbers of cases are being highlighted. 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 (2). When uncomplicated by inflammation the lesion appears firm, pale pink and resilient with a minutely lobulated surface and no tendency to bleed. 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 (4). Very few cases of amlodipine induced gingival enlargements have been reported till date (5-7), as a result of which it continues to be vastly prescribed. This presentation of 5 cases attempts to bring to light the existence of this adverse effect with the use of Amlodipine not as a rarity but a routinely observed finding in patients who have been prescribed this drug for various cardiac conditions. The patients discussed were on different doses of amlodipine either alone or in conjunction with other groups of anti-hypertensives. The effect of the dose of amlodipine on the severity of gingival enlargement was also assessed.

Case Series

All of the five cases presented to the dental office with a similar complaint of generalized swelling in the gums with bleeding and suppuration from them. On evaluating their medical histories all of them were hypertensives and on amlodipine therapy. The first case was of a 45 year old lady who gave a positive history of hypertension and hypothyroidism and was on medication for the same. On exploring further the anti-hypertensive drug identified was amlodipine 10mg (Amlopress®) taken daily since last one year and Thyroxine 100 microgram (Thyronorm®). On clinical examination, a large bulbous enlargement of the gums was seen in relation to left lower lateral inci-



Fig. 1. Photograph showing clinical presentation of Case No.1

isor and canine region. The swelling involved the marginal gingiva, inter-dental papilla as well as the attached gingiva and extended into the vestibule. On examining the rest of the oral cavity, the marginal and inter-dental gingiva of almost all the teeth were enlarged especially in the maxillary and mandibular anterior region with a superimposed inflammatory component. (Fig. 1)

The second case was that of a 60 year old man who presented to the out-patient department with a chief complaint of swelling in the gums in relation to the left lower back tooth region since 6 months. The swelling was painful on mastication and interfered with the placement of the patient's removable prosthesis. Medical history revealed the patient to be hypertensive and was taking amlodipine 5mg as a single daily dose since 2 yrs. Clinical examination revealed that the marginal and inter-dental papillary gingival tissues were enlarged especially in relation to the upper and lower anterior teeth. The tissues appeared firm and fibrotic with a mulberry appearance on the surface. Additionally, a large bulbous enlarged gingiva around the left lower third molar region extending from the mesial aspect adjoining an edentulous space to the buccal and distal aspect of the third molar was seen. (Fig. 2)

The remaining three cases were on a combination of amlodipine 2.5mg and atenolol 25 mg once daily since



Fig. 2. Photograph showing clinical presentation of Case no. 2

Case No.	Age	Sex	Treatment time with Amlodipine	Dose of Amlodipine	Presence of other diseases	Other drugs prescribed (dose /day)	Treatment rendered
1.	45 yrs	Female	One year	10mg	Hypothyroidism	Thyroxin 100 microgram	<ul style="list-style-type: none"> • Plaque control measures • Oral hygiene instructions • Scaling/ root planing • Internal bevel gingivectomy with flap surgery • Regular maintenance & periodic follow up.
2.	60 yrs	Male	Two years	5 mg	Nil	Nil	
3.	65 yrs	Female	Five years	2.5mg	<ul style="list-style-type: none"> • Type II Diabetes Mellitus • Angina 	<ul style="list-style-type: none"> • Atenolol 25mg • Metformin 1000 mg • Ecosprin 75 mg • Atorvastatin 	
4	45 yrs	Female	Two years	2.5 mg	Nil	Nil	
5.	55 yrs	Female	Three years	2.5 mg	Nil	Nil	

Table 1. Details of the demographics, medical history and treatment of the clinical cases

2-3 years. The first of these cases was additionally diabetic and also gave a history of angina 3 years back. This patient had been prescribed various drugs due to the prevailing cardiac condition. The other two cases were only hypertensive with no other systemic complicating factors. Clinical evaluation revealed diffuse gingival overgrowth especially in relation to upper and lower anterior teeth, and also involving the marginal and inter-dental papilla of the posterior regions. Bleeding on probing and suppuration were elicited with presence of copious plaque and calculus deposits. (Fig. 3a) The clinical details of the cases have been tabulated. (Table 1)

Based on clinical evaluation and radiographic assessment a provisional diagnosis of amlodipine induced drug enlargement superimposed with inflammation was established. Phase-I periodontal therapy comprising mechanical and chemical removal of plaque and calculus as well as patient instructions on oral hygiene maintenance was initiated. The patient was simultaneously advised to seek medical consultation. Following oral prophylaxis and substitution of amlodipine, significant improvement in the gingival tissues was observed (Fig. 3b). However, the OPG X-rays of these patients revealed the presence of generalized underlying bone loss. The gingival contours were un-esthetic, difficult to maintain and favored plaque accumulation leading to further destruction of the attachment apparatus. Hence, phase II periodontal therapy was performed with an internal bevel gingivectomy and flap operation. The tissues excised were duly sent for histo-pathological assessment which revealed the presence of parakeratinized epithelium with acanthosis and elongated rete-pegs, connective tissue fibrosis with inflammatory cells, few scattered giant cells and capillaries indicating a superimposed inflammation. This further confirmed our diagnosis of drug associated gin-

gival enlargement. Post-operative evaluations revealed that good physiological contours for the patient had been achieved favoring good plaque control.

Discussion

Calcium channel blockers comprise of three chemical



Figure 3. A. Photograph showing clinical presentation of Case no. 3
B. Photograph showing Case No. 3 two months following amlodipine substitution and phase I therapy.

families viz. dihydropyridines including nifedipine, amlodipine, felodipine etc., phenylalkylamines which includes verapamil and benzothiazepines which includes diltiazem. Compared to conventional therapy (diuretics and beta blockers), calcium channel blockers have been found to be more effective and hence these are more frequently prescribed (1). The dihydropyridines have been found to be associated with enlargement of the gums with nifedipine having the highest incidence of about 6% (3). Amlodipine however is also being found to be associated with gingival overgrowth and more and more such cases are being reported. A recent study comparing the effect of calcium channel blockers vis-à-vis Renin angiotensin system drugs showed a twofold greater enlargement of the gums with the current use of the former category of drugs. This association was dose dependant and greatest for dihydropyridine derivatives (8). In the case series presented, different doses of amlodipine did not correlate with the severity of the clinical presentation.

The underlying mechanism for the pathogenesis of this gingival over-growth remains to be fully understood. These drugs which affect intracellular calcium metabolism or transport may in some patients stimulate gingival fibroblasts to cause increased deposition of extracellular matrix components, such as glycosaminoglycans (2). The other proposed non-inflammatory mechanisms include defective collagenase activity, blockage of aldosterone synthesis in adrenal cortex which is also calcium dependent and causes a consequent feedback increase in ACTH level (9), and up-regulation of the keratinocyte growth factor (10). Alterations in the cytokine balances may contribute more significantly to the development and maintenance of gingival overgrowth. Proliferation and differentiation of connective tissue cells and production of extracellular matrix are controlled by cytokines that initiate signaling cascades mediated by specific receptors. Recent studies have demonstrated abnormally high levels of specific cytokines such as IL-6, IL-1beta, platelet derived growth factor (PDGF-B), Fibroblast growth factor (FGF-2), Transforming growth factor (TGF-beta) and connective tissue growth factor (CTGF) in gingival overgrowth tissues (11).

Drug induced gingival enlargements are usually associated with a superimposed inflammatory component which has to be minimized as it is a major contributor to the gingival overgrowth (12). Scrupulous oral hygiene maintenance by effective plaque control strategies both home care and professional need to be taken care of. This helps in decreasing the degree of gingival overgrowth present, improves overall gingival health and helps maintain attachment levels. In cases with severe gingival overgrowth one needs to consider the substitution of amlodipine with isradipine, lercanidipine and lacidipine which are the newer fourth generation dihydro-

pyridines or other classes of anti-hypertensives such as beta blockers, A.C.E inhibitors or thiazide derivatives. Discontinuing the causative drug has been found to reduce the gingival overgrowth (13), however, to assist the patient in plaque control as well as from an esthetic point of view surgical correction may be deemed necessary. Cases in which there is no underlying bone loss, external bevel gingivectomy and gingivoplasty is done. In cases with presence of attachment loss and underlying osseous defects, a procedure called internal bevel gingivectomy with flap operation is performed so as to be able to resect the gingival overgrowth and in addition treat the underlying osseous defects (12, 14). All of the five cases that are presented had some degree of moderate to severe alveolar bone loss and hence internal bevel gingivectomy was the treatment of our choice. The patients were followed up for a period of up-to one year and with drug substitution and plaque control, no recurrences were seen. On clinical assessment, the effect of amlodipine on gingival tissues was probably not dose related because even 2.5mg of amlodipine had resulted in a significant gingival enlargement. This probably contradicts Jorgenson's study on cardiac patients taking amlodipine at a dose of 5mg/day and showing no incidence of gingival overgrowth (15). Importance of plaque control needs a special emphasis here as it could be a major contributing factor for accentuating the enlargement even at low serum levels of amlodipine.

Conclusions

One needs to abreast this issue to the various medicine experts to bring this fact to light and to minimize the prescriptions or practice care while prescribing the innocuous appearing Amlodipine. Even with minimal dose of amlodipine a significant gingival enlargement is seen hence, regular follow up with suitable dental referral for evaluating gingival and periodontal status becomes imminent. Dental professionals need to identify and then guide the patient to seek necessary medical intervention.

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