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Research Paper

Periodontal Management Of Amlodipine-Induced gingival Over Growth: A 2 Years Follow-Up Case Report

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***ABSTRACT*:** *Gingival overgrowth (GO) is one of the most important clinical features of gingival pathology. It has been found to be 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 new 3rd generation calcium channels blocker, has also been found to exhibit this adverse effect with very few cases reported till date. The effect of the dose of amlodepine on the severity of gingival enlargement needs to be assessed.*
This paper presents a case report of an 63 years old female with gingival over-growth as a side effect of a 10 mg per day therapy with amlodepine. A brief review on the pathogenesis of this condition, commonly associated with etiological mechanisms and sequence of periodontal therapy rendered have also been included.
Gingival enlargement continues to be a predominant side effect of calcium channel blocker. The accentuated gingival contours accumulate plaque leading to the destruction of the underlying periodontium. Dental professionals need to identify and then guide the patient to seek necessary medical intervention.
Keywords -*Amlodipine, Flap surgery,Gingival overgrowth, Gingivectomy, Nifedipi*

I. INTRODUCTION

Gingival overgrowth (GO) is defined as abnormal growth of maxillary and mandibular gingiva. It is one of the most important clinical features of gingival pathology. It may cause aesthetic changes and clinical symptoms such as pain, speech disturbances, abnormal tooth movement, dental occlusion problems, enhanced risk of caries and periodontal disorders. [1]
It has multifactorial etiology and is often connected with inflammatory changes in the gingiva. Today, Gingival enlargements are commonly seen as a side effect of various groups of medications which includes: Anticonvulsants, anti-hypertensives; esp. Calciumchannel 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 [2,3]. Although their pharmacologic effects are different and targeted to different tissues, they exhibit the same effect on the gingival connective tissue, causing identical clinical and histopathological changes. Those changes were defined as “gingival hyperplasia” or “gingival hypertrophy”, but today the widely-spread term, which refers to all types of drug-induced lesions, is gingival overgrowth.

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 [1]. 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].
The incidence of gingival enlargement with amlodipine was reported to be much lesser than nifedepine. Jorgensen, 1997 had reported the prevalence of amlodipine-induced gingival enlargement as 3.3% [5]. However recently large numbers of cases are being highlighted. Clinically, the enlargement is usually seen 3-6 months following the initiation of the concerned drug [6].

First reports for amlodipine-induced overgrowth are from Ellis et al [7] and Seymour et al. [8]. Laftzi et al [9] reported rapidly developed gingival hyperplasia in patient, received 10 mg amlodipine only two months after taking the drug.

The mechanisms behind the GO are not well known. An inflammatory and a non-inflammatory mechanism have been suggested, the non-inflammatory theory suggests a defective collagenase activity due to an increased uptake of folic acid (Brown et al. 1990), a blockage of aldosterone synthesis in adrenal cortex with a consequent feedback increase in adrenocorticotropic hormone (ACTH) levels (Nyska et al.1994) and an up-regulation of keratinocyte growth factor (Das & Olsen 2000). The inflammatory theory suggests This inflammation may lead to an up-regulation of several cytokine factors and in particular the transforming growth factor beta 1 (TGF-b1) (Border &Noble 1994).In a recent review of the signaling pathways of gingival fibroblasts, it is suggested that the molecular and cellular characteristics of GO differ considerably as a function of the causative drug (Trackman & Kantarci 2015).[10] that inflammation develops as a result of a direct toxic effect of concentrated drugs in the gingival crevicular fluid, possibly in connection with bacterial plaque (Van der Vleuten et al. 1999).[11]
Still, there is not so much investigations for the amlodipine-induced overgrowth prevalence [6], nor clinical trials [12].

The presentation of this case attempts to bring to light the existence of this adverse effect with the use of Amlodepine not as a rarity but a routinely observed finding in patients who have been prescribed this drug for various cardiac conditions.

II. CASE PRESENTATION

A 63-year-old female was referred to the Department of Periodontia of Rabat Dental College and Hospital, with chief complaints of gingival enlargement with foul odor, bleeding, suppuration and fetid discharge from gums, unsatisfactory esthetics and difficulty for maintaining the oral hygiene since 1 year.
Patient was hypertensive and non-insulin-dependent diabetic with history of taking amlodipine 10 mg once daily (dipicor® 10mg) since last 3 years, hydrochlorothiazide 5mg(trithazideRampiril®),Metformine 1g(ADO®) and gliclazide 30 mg(diamicron®) once daily.

Intraoral examination revealed poor oral hygiene with abundant supra- and subgingival plaque and calculus, Severe halitosis was observed. 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 massive gingival enlargement at the vestibular surface of lower right second molar extending from the mesial aspect to the buccal and distal region. (fig 1, fig 2). Probing pocket depth was more than 7 mm in most periodontal sites. There was profuse bleeding on probing and signs of active inflammation-suppuration in some sites

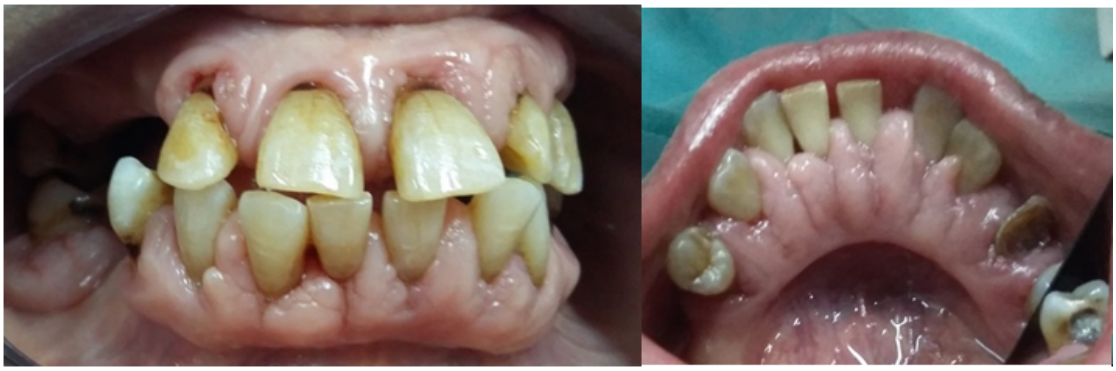
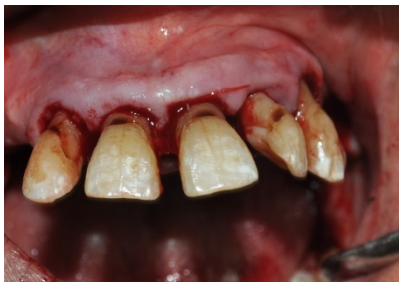


Figure 1 : Photographies showing clinical presentation at first visit



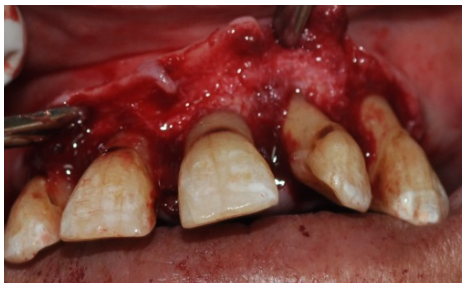


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Figure 2: Photography after correction of gingival overgrowth by internel bevel gingivectomy and flap procedure

Based on clinical evaluation and radiographic assessment a provisional diagnosis of amlodepine induced drug enlargement superimposed with inflammation was established. Phase-I periodontal therapy comprising physician consultation, who reduced dose of amlodipine to 5 mg/ once daily, and mechanical and chemical removal of plaque and calculus as well as patient instructions on oral hygiene maintenance was initiated. significant improvement in the gingival tissues was observed. However, the 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, connective tissue fibrosis and inflammatory cells and capillaries indicating a superimposed inflammation. This further confirmed our diagnosis of drug associated gingival enlargement.

Post-operative evaluations, all of 3 months, revealed that good physiological contours for the patient had been achieved favoring good plaque control.

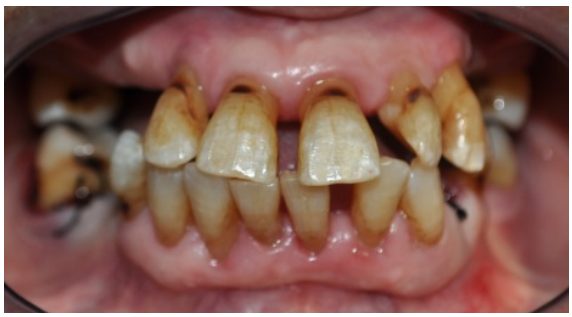

Figure 3: Photograph showing heeling in 6 months postoperative

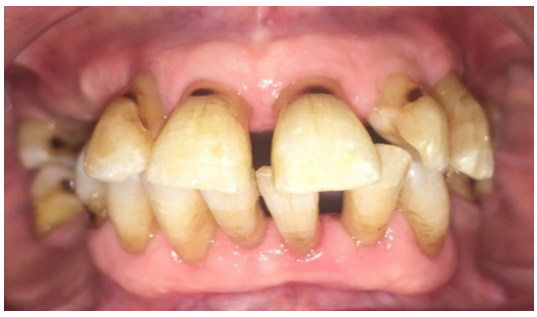

Figure 4: Photograph showing heeling 2years postoperative

III. DISCUSSION

Calcium channel blockers comprise of three chemical families viz. dihydropyridines including nifedepine, 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 [12]. The slow elimination ensures long-term action even after a single dose administration (5 or 10 mg). That is why amlodipine is preferred both from patients and physicians. The dihydropyridines have been found to be associated with enlargement of the gums with nifedepine having the highest incidence of about 6% [6].

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Amlodipine however is also being found to be associated with gingival overgrowth and more and more such cases are being reported.

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 [13]. The other proposed non-inflammatory mechanisms include defective collagenase activity, blockage of aldosteronesynthesis in adrenal cortex which is also calcium dependent and causes a consequent feedback increase in ACTH level [14], and up-regulation of the keratinocyte growth factor [15]. 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 [16,17].

The first step of GO management should be drug substitution (with another effective one, but from different group), or reduction of amlodipine dose, then the treatment should start with initial conservative periodontal therapy. The effective plaque control is very important basic procedure. The interaction between the drug and the gingival tissues could be enhanced by gingival inflammation, caused by pour oral hygiene. Although the exact role of the periodonto-pathogens in the etiology and pathogenesis of the overgrow this not quite clear, their elimination and regular maintenance of strict oral hygiene is of crucial importance for the healing process of gingival tissues. When drug substitution, or reduction and the initial periodontal therapy do not provide satisfactory clinical response, as our case, surgical management, may be indicated. This procedure includes the scalpel gingivectomy-gingivoplasty, overgrowth flap surgery, electro-surgery and laser excision. The aim of this procedure is to restore the anatomical contour and the gingival margin [18].

In our case, we opted for gingivectomy with flap surgery to resect the gingival overgrowth and in addition treat the underlying osseous defects. Marvogiannis et al., 2006 suggested that there may be recurrence of gingival enlargement, if medication is continued and also persistence of other risk factors [18]. In our case, no recurrence was noted, after a 2 years follow-up.

IV. CONCLUSION

In conclusion, the amlodipine, one of the recently developed calcium channel blockers induced gingival overgrowth. This case history shows that, in addition to reduction of the drug, plaque control was very important in helping to improve the periodontal condition. For many patients, surgery is the treatment of choice. Preventing recurrence of overgrowth is a significant challenge to the Periodontist, regular follow up with suitable dental referral for evaluating gingival and periodontal status becomes imminent.

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