

Amlodipine-induced Gingival Hyperplasia – A Case Report and Review

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ABSTRACT

Anticonvulsants, antihypertensive calcium channel blockers and immunosuppressants are the three main classes of drugs known to cause drug-induced gingival hypertrophy or hyperplasia. Among the calcium channel blockers, nifedipine administration has most frequently been associated with medication-related gingival hyperplasia. The incidence with amlodipine, which has a mode of action pharmacodynamically comparable to nifedipine, has rarely been reported. Here, we present a rare case of amlodipine-induced gingival hyperplasia in a hypertensive patient.

Keywords: Amlodipine, calcium channel blockers, gingival enlargement, gingival hyperplasia

Hiperplasia Gingival inducida por Amlodipina – Reporte de una Caso y Revisión

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RESUMEN

Los anticonvulsivos, bloqueadores antihipertensivos de los canales de calcio, y los inmunosupresores son las tres clases principales de medicamentos conocidos por su posibilidad de causar hiperplasia o hipertrofia gingival inducida por medicamentos. Entre los bloqueadores de los canales de calcio, la nifedipina ha sido la más frecuentemente asociada con la hiperplasia gingival relacionada con medicamentos. La incidencia con la amlodipina, que tiene un modo de acción farmacodinámicamente comparable con la nifedipina, ha sido raramente reportada. Aquí, presentamos un caso raro de hiperplasia gingival inducida por amlodipina en un paciente hipertenso.

Palabras claves: Amlodipina, bloqueadores de los canales del calcio, agrandamiento gingival, hiperplasia gingival

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INTRODUCTION

There is an ever-increasing number of medications which may induce overgrowth of the gingiva, although a large range of pathological and idiopathic reactions can also result in gingival overgrowth. 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 (1, 2).

Terms such as gum hypertrophy or gum hyperplasia go hand in hand but they are the histopathological diagnosis of gum enlargement. Gum enlargement has multiple causes. Drugs are amongst the most common culprit. Drug-induced enlargement has been associated with a patient's genetic pre-

disposition (3, 4). Currently, more than 20 prescription medications are associated with gingival enlargement (3, 5). Three main classes of drugs are anticonvulsants, immunosuppressives and antihypertensive agents (3, 6).

Amlodipine, a newer agent of dihydropyridine, used for treatment of hypertension and angina, was first reported for causing gingival overgrowth as a side effect by Seymour *et al* in 1994 (7, 8). Lafzi *et al* had reported rapid development of gingival hyperplasia in patients who received 10 mg per day of amlodipine within two months of onset (9). Clinical manifestation of gingival enlargement frequently appears within one to three months after initiation of treatment with the associated medication (7, 10).

Pharmacological profile of amlodipine:

- Long-acting dihydropyridine (other members: nifedipine, nicardipine, isradipine, nitrendipine and felodipine)
- Mechanism of action: coronary and peripheral arterial vasodilatation

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- Dosage: 2.5 or 5 grams, single dose (alone or in combination with atenolol)
- Adverse effects: headaches, facial flushing, dizziness, oedema, gingival hyperplasia
- Oral effects: detectable in gingival crevicular fluid
- Significant sequestration of drug in patients exhibiting gingival overgrowth (11, 12)

There are less data on reports of hyperplasia with amlodipine at a dose of 5 mg, even after taking for more than six months (6, 7). Here, we report a rare case of massive gingival hyperplasia in a hypertensive patient who is under amlodipine therapy since six months.

CASE REPORT

A 48-year old male patient reported to the Department of Oral Medicine and Radiology, with a chief complaint of swelling in the upper and lower gums for three months. History revealed that the patient was diagnosed with hypertension six months previously and amlodipine (5 mg) was prescribed. At three months, the patient noticed the gingival enlargement and intermittent bleeding of the gums. On general examination, the patient was moderately built and nourished. Intraoral examination revealed diffuse enlargement of the gingiva of both the upper and the lower jaws involving marginal gingiva, attached gingiva and the interdental papilla (Fig. 1).



Fig. 1: Clinical photograph showing frontal view of gingival enlargement.

The attached gingiva was erythematous (Fig. 2), the surface was lobulated, and showed bleeding on probing. The probing depth of the gingival sulcus was recorded to be in the range of 4 mm to 6 mm (Fig. 3).

The maxillary and mandibular anterior teeth showed diastema with labioversion of the mandibular left lateral incisor and canine and linguoversion of mandibular right and left central incisors (Figs. 4, 5). Occlusion revealed anterior open bite (Fig. 1).

Panoramic radiography revealed full complement of maxillary and mandibular teeth, generalized spacing in the maxillary and mandibular anterior region, generalized horizontal bone loss and angular bone loss with respect to mandibular left first molar (Fig. 6).



Fig. 2: Clinical photograph of the gingival enlargement (lateral view).

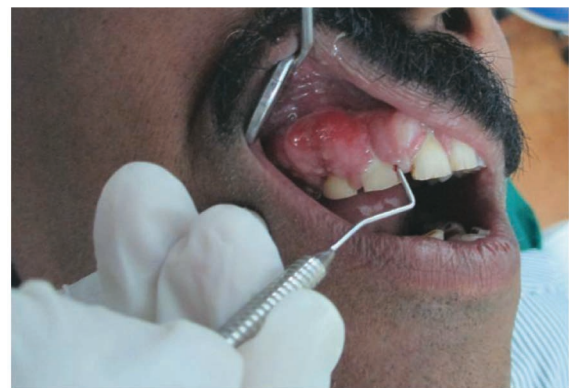


Fig. 3: Clinical photograph showing probing depth.



Fig. 4: Clinical photograph showing gingival overgrowth in the palatal aspect and interdental areas. Also observe interdental spacing.



Fig. 5: Clinical photograph showing gingival enlargement in the lingual aspect of the mandibular arch. Also observe the labiolingual displacement of the mandibular anterior teeth.



Fig. 6: Panoramic radiograph of the patient showing multiple areas of vertical and horizontal bone loss.

The patient was advised regarding the gingival hyperplasia and the effects of the medication he had been taking for six months. He was advised on surgical periodontal treatment for aesthetic reasons and functional problems since the enlargement had not shown any significant changes after professional debridement with scaling and root planning. The patient was not willing to undergo any surgical intervention.

DISCUSSION

Amlodipine is a second-generation dihydropyridine calcium channel blocker that can cause gingival hypertrophy. The prevalence of amlodipine-induced gingival hypertrophy has been shown to be between 1.7% and 3.3%. The incidence of gingival hypertrophy with nifedipine therapy has been reported to be as high as 20%, and a 2002 study reported that the prevalence with the use of calcium channel blockers might be as high as 38%. Gingival hypertrophy is 3.3 times more common in men than in women (13, 14).

Although the mechanisms of action may be different, the clinical and microscopic appearance of drug-induced gingival enlargement is similar with any drug. It begins as a firm, nodular enlargement of the interdental papilla, within three months of taking enlargement inducing medicines, which is limited to keratinized portions of the gingiva. The target cell is the gingival fibroblast, as all lesions are characterized by an increase in the connective tissue component. Gingival inflammation also appears to be an important predisposing factor to this unwanted effect. This suggests that the lesion is a consequence of the interaction between gingival fibroblasts, cellular and biochemical mediators of inflammation and drug metabolites (15, 16).

Drug-induced gingival enlargement as a possible side effect has been reported with systemic use of anticonvulsants, immunosuppressants (like cyclosporine) and calcium channel blocking agents (like nifedipine). There are also case reports on gingival overgrowth associated with erythromycin and trimethoprim sulphamethoxazole. Among the anticonvulsants, gingival enlargement is seen mostly with phenytoin (diphenyldydantoin) and rarely with vigabatrin, sodium valproate, primidone and phenobarbital. Among the calcium channel blockers, gingival enlargement is most commonly associated with nifedipine and also with amlodipine, verapamil, nicardipine, nitrendipine, oxodipine, felodipine and diltiazem (15). None of the medications listed above was concomitantly used by our patient during the mentioned period.

Poor oral hygiene is an important risk factor for the expression of drug-induced gingival overgrowth (17, 18). Most reports on the relationship between bacterial plaque and gingival overgrowth have been derived from cross-sectional studies, but there is no clear evidence that bacterial plaque is a contributory factor or a consequence of the gingival changes (17). The underlying mechanism of gingival enlargement still remains to be fully understood. However, two main inflammatory and non-inflammatory pathways have already been suggested (19–21). The proposed non-inflammatory mecha-

nism includes defective collagenase activity due to decreased uptake of folic acid, blockage of aldosterone synthesis, in adrenal cortex and consequent feedback increase in the adrenocorticotrophic hormone level and upregulation of keratinocyte growth factor. Alternatively, inflammation may develop as a result of direct toxic effects of concentrated drug in crevicular gingival fluid and/or bacterial plaques. This inflammation could lead to the upregulation of several cytokine factors such as transforming growth factor-beta 1 [TGF- β 1] (9, 19, 22).

Current studies on the pathogenetic mechanism of drug-associated enlargement are focussing on the direct and indirect effects of these drugs on gingival fibroblast metabolism. Because only a subset of patients treated with this medication will develop gingival overgrowth, it has been hypothesized that these individuals have fibroblasts with an abnormal susceptibility to the drug. It has been shown that fibroblast from overgrown gingiva in these patients are characterized by elevated levels of protein synthesis, most of which is collagen. It also has been proposed that susceptibility or resistance to pharmacologically-induced gingival enlargement may be governed by the existence of differential proportions of fibroblast subsets in each individual which exhibit a fibrogenic response to this medication (12).

Treatment is generally targeted on drug substitution and effective control of local inflammatory factors such as plaque and calculus (12, 23). 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 (12). The need for, and timing of, any surgical intervention needs to be carefully assessed. Surgery is normally performed for cosmetic/aesthetic needs before any functional consequences are present (1, 23, 24). Most reports of amlodipine gingival overgrowth have required surgical intervention (25).

The use of carbon dioxide lasers has shown some utility for reducing gingival enlargement, an approach which provides rapid postoperative haemostasis. Consultation with the patient's physician prior to surgical treatment regarding antibiotic and steroid coverage should take place in the immunosuppressed patient (12, 24). The carbon dioxide laser has a wavelength of 10 600 nm, is readily absorbed by water and therefore very effective for the surgery of soft tissues, which have a high water content. Blood vessels in the surrounding tissues up to 0.5 mm are sealed (26). Thus the advantages of laser over the scalpel are the strong haemostatic and bactericidal effect and the provision of a relatively dry field for improved visibility (27).

Finally, the emphasis is that gingival overgrowth could be a side effect of amlodipine even with a very short term and low dose administration (20).

CONCLUSION

Dental surgeons should be able to identify the changes in the oral cavity related to the general health of their patients. Patients must be informed of the tendency of certain drugs to

cause gingival enlargement and the associated oral changes and the importance of effective oral hygiene.

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