AMLODIPINE-INDUCED GINGIVAL OVERGROWTH: A CASE REPORT

Abstract
Gingival enlargement is a known side effect of calcium channel blockers especially the dihydropyridine group. Among the calcium channel blockers, gingival enlargement has most frequently been described as a side effect following administration of nifedipine. The incidence with amlodipine is much lower; however, there have been few reports showing the association of this drug with gingival enlargement. It causes aesthetic disfigurement, speech disturbances, abnormal tooth movement and difficulty in mastication. In this article, a case of amlodipine induced gingival overgrowth has been presented which was managed with the conservative approach. The treatment aspect included Phase-1 therapy, substitution of the drug, and the maintenance and supportive therapy resulting in excellent clinical outcome.

KEY WORDS: Drug Induced Gingival Enlargement, Amlodipine, Gingival Overgrowth, Calcium channel Blockers, Conservative approach

INTRODUCTION
Gingival enlargement” or “gingival overgrowth” are the preferred terms for all medication-related gingival lesions previously termed "gingival hyperplasia" or “gingival hypertrophy. Patients medicated with certain drugs may be implicated in this unwanted side effect that is drug induced gingival overgrowth, which may interfere with aesthetics, mastication or speech. Various pharmacological agents responsible for such a side effect include phenytoin, cyclosporine, calcium-channel blockers (nifedipine, verapamil, diltiazem, oxodipine, amlodipine) and antibiotics (erythromycin).While a prevalence approximately of 50% is described with phenytoin, the rate for cyclosporins and calcium channel blockers is only about 5% to 30%. The prevalence of gingival overgrowth in patients taking amlodipine was reported to be 3.3% (Jorgensen, 1997) which is lower than the rate in patients taking nifedipine, 47.8% (Nery et al., 1995). This can have a significant effect on the quality of life as well as increasing the oral bacterial load by generating plaque retention sites.

The pathogenesis of drug influenced gingival enlargement suggest that it is multifactorial including: age, genetic predisposition, pharmacokinetic variables, drug induced alterations in gingival connective tissue homeostasis,
plaque induced inflammatory changes and drug induced action on growth factors. The effects of these drugs are not only directed at the primary target tissues but also on secondary target tissues, such as gingival connective tissue, causing clinical and histopathological aberrations. Seymour et al were the first to report amlodipine-induced gingival overgrowth, and there have been only few reported associations of gingival overgrowth with this drug.

It starts as a painless, beadlike enlargement of the interdental papilla and extends to facial and lingual gingival margins. It may partially or completely cover the tooth surfaces. If there is underlying periodontal disease then the tissues may appear inflamed. It tends to be more severe in areas where plaque accumulates. Otherwise the gingival enlargement is distributed symmetrically and for the anterior teeth to be more severely affected than the posterior teeth. The diagnosis is mainly based on the medical history, clinical features and histopathological features.

It clinically presents as enlarged interdental papillae and resulting in a lobulated or nodular morphology. The presence of the enlargement makes plaque control difficult, often resulting in a secondary inflammatory process that complicates the gingival overgrowth caused by the drug.

In this article, a case of amlodipine induced gingival overgrowth has been presented wherein the AIGO was treated in the following phases:

(1) Thorough Phase-1 therapy

(2) Substitution of the drug

(3) Maintenance and supportive therapy

CASE REPORT

A 55-year-old male patient reported to the outpatient department of Periodontology and Oral Implantology of Sri Guru Ram Das Institute of Dental sciences and Research Amritsar, with a chief complaint of pain and swelling in the gums and bleeding while eating and brushing of teeth, which had been progressively increasing over the previous 6 months (Image 1). None of his family members had this kind of enlargement.

A medical history of the patient revealed that the patient was hypertensive and taking antihypertensive drug, amlodipine (2.5 mg/day, single dose orally) since 72 months. The patient noted a gradual enlargement of the gingiva of 24 months duration. Dental history revealed that the patient had undergone scaling 18 months ago, after which there was only little reduction.

The patient’s medical history revealed that he had been hypertensive for 6 years. Intraoral examination revealed generalized pink gingiva with rolled out gingival margins, lobulated papillae, and fibrous overgrowth throughout the maxilla and mandible, particularly on the labial and buccal side (Image 2). Generalized deep pockets, exudation on application of digital pressure, and bleeding on probing were noted (Image 3). The oral hygiene status of the patient was poor, accompanied by marked plaque and calculus accumulation around all teeth. A provisional diagnosis of
drug-induced gingival enlargement was made for the patient.

**Investigations**

Complete Haemogram was normal. Intra-oral periapical radiograph showed generalized mild bone loss.

**Provisional diagnosis**

Based on clinical presentation and past history, a diagnosis of Amlodipine Influenced Gingival Enlargement was made.

**Management**

Referral to the physician: Amlodipine 2.5 mg/day was replaced with Atenolol 50 mg/day.  

Phase I therapy: Scaling and root planing, along with meticulous oral hygiene maintenance (including 0.2% chlorhexidine use) by the patient (Image 4).  

Maintenance phase: First after 15 days for 1 month then at an interval of 3 months for 6 months (Image 5).

**DISCUSSION**

Amlodipine is a dihydropyridine calcium antagonist that inhibits the transmembrane influx of calcium ions into vascular smooth muscle and cardiac muscle. It is frequently used as an antihypertensive and for the treatment of angina.

Mild hyperplasia was detected with amlodipine with a prevalence rate of 3.3%. Tejnani et al (2014) suggested that bacterial inflammation, resulting from dental plaque, is essential for gingival hyperplasia induced by amlodipine. Therefore, higher the Plaque Index, more severe will be the hyperplasia. Considering the predominance of lymphocytes, plasma cells, and mast cells in the connective tissue, the significant role of inflammation in the incidence and severity of gingival hyperplasia will be more obvious.

The difference in the occurrence of enlargement between nifedipine and amlodipine is of interest, since both drugs are dihydropyridines and hence structurally similar. However, two drugs differ in a way that, amlodipine is more polar than other dihydropyridines, with pKa value 8.7. Thus the drug may not pass through cell membrane without an active transport mechanism. By contrast, nifedipine is intensely lipophilic and will dissolve readily within the cell membrane and pass into the cytoplasm. The majority of amlodipine will be tissue bound (and hence inactive) rather than circulating freely in the blood giving better patient compliance, and has until now been associated with similar or reduced severity of side effects compared to nifedipine. Amlodipine, like nifedipine, can be detected in gingival crevicular fluid, and gingival sequestration of amlodipine associated with gingival hyperplasia has also been reported.

Most drug-associated gingival enlargements appear to be clinically indistinguishable, with the possible exceptions of CsA and phenobarbinate. In phenobarbitone-treated patients, the gingiva may be enlarged uniformly without lobulations of the interdental papillae, and severity of the clinical lesions has been reported to be greater in the posterior as compared to the anterior regions. In individuals immunosuppressed with CsA, sometimes pebbly or papillary lesions appear on the surface of larger lobulations, which have been associated with the presence of candida hyphae invading the gingival epithelium.

The treatment options for drug-induced gingival enlargement should be based on the medication being used and the clinical presentation of the individual case. First, consideration should be given to the possibility of discontinuing the drug or an alternate drug. The classical surgical approach has been the external bevel gingivectomy. However, a total or partial internal gingivectomy approach has been suggested as an alternative. In the present report, as the gingival overgrowth was not associated with the true periodontal pockets and the osseous defects and it responded well to the scaling and root planing, only phase 1 therapy was carried out.

Finally, it should be noted that one question still remains ambiguous, i.e., why is it that despite there being similar conditions concerning plaque and amlodipine dosage, some of the drug receivers become affected with hyperplasia and others do not? Probably, this can be attributed to the biological differences among human beings, such as the existence of different subgroups of gingival fibroblasts. Therefore, investigating the interactions between factors such as the metabolism of gingival fibroblast subgroups, hormonal effects and growth agents can be a guide to discover such differences.

**Conclusion**

The reported case is an example of a combined type of gingival enlargement basically a drug-induced one, complicated by inflammatory changes due to plaque accumulation. Treatment should focus 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.

**REFERENCES**

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