Amlodipine Induced Gingival Enlargement Revisited

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ABSTRACT

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Gingival enlargement or gingival overgrowth appears from mild to bizarre clinical presentations. It can be due to an umpteen number of causes. Drug induced gingival enlargement is one among them. The three most common categories of drugs causing gingival enlargement are Anticonvulsants, Calcium channel blockers and Immunosuppressant. Calcium channel blockers are one of the most commonly used drugs for the management of cardiovascular disorders and are known for causing gingival over growth as adverse effects. Now a days, a new drug in this family Amlodipine, is being widely used, because of its duration of action. But it is of concern to the dental practitioner that this drug too has a similar effect on gingival tissues. This paper aims at drawing the attention of general medical practitioners, cardiologists and dentists towards the adverse effects of Amlodipine along with providing a brief review of the pharmacologic profile of this drug, its effects on the gingiva and the management of gingival enlargement

Keywords: Drug induced, gingival enlargement

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INTRODUCTION

Gingival enlargement or gingival overgrowth" is the preferred term for all medication-related gingival lesions previously termed "gingival hyperplasia" or" gingival hypertrophy." These earlier terms did not accurately reflect the histologic composition of the pharmacologically modified gingiva.

CLASSIFICATION

I. Inflammatory enlargement
   a. Chronic
   b. Acute
II. Drug-induced enlargement
III. Enlargements associated with systemic diseases or conditions
   A. Conditioned enlargement
      a. Pregnancy
      b. Puberty
      c. Vitamin C deficiency
      d. Plasma cell gingivitis
   B. Nonspecific conditioned enlargement
      a. pyogenic granuloma
   C. Systemic diseases causing gsingival enlargement
   a. Leukemia
   b. Granulomatous diseases (e.g., Wegener's granulomatosis, sarcoidosis)
IV. Neoplastic enlargement (gingival tumors)
   A. Benign tumors
   B. Malignant tumors
   C. False enlargement

DRUG INDUCED GINGIVAL ENLARGEMENT

EPIDEMIOLOGY

Not all the patients using these agents are affected by gingival overgrowth, and the extent and severity are variable in such patients. Phenytoin-induced overgrowth may be present in 50 to 100% of patients treated with such drug, whereas cyclosporin and calcium channel blocker-induced overgrowths seem to be less common, ranging from 15-85% and 10-30% respectively. Although gender and age may not be relevant risk factors for phenytoin-induced overgrowth, among patients taking cyclosporin and/or nifedipine, males may be at higher risk than female.

The relationship between age and gingival overgrowth is uncertain; some authors have described young age as risk factor, but other studies have not confirmed such finding. Age is not an applicable risk factor for the calcium channel blockers since the use of the drugs is usually confined to the middle aged and older adult. Nevertheless, in patients treated with both cyclosporin and calcium channel blockers, age has been identified as a risk factor.

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A correlation with dosage, duration, drug concentrations (in blood and whole saliva) and severity/extent of gingival enlargement has also been suggested, but so many variables (sampling technique, pharmacokinetic factors) can influence this aspect, that it remains controversial. However, it has been recently reported that patients treated with cyclosporin solution experience earlier onset of gingival changes and more extensive overgrowth than patients using capsules.[1]

An increasing number of medications are associated with gingival enlargement. Currently, more than 20 medications are associated with gingival enlargement. Drugs associated with gingival enlargement can be broadly divided into three categories: anticonvulsants, calcium channel blockers immunosuppressants. Although pharmacologic effect of each of these drugs is different and directed toward various primary target tissues, all of them seem to act similarly on secondary target tissue, i.e., the gingival connective tissue, causing common clinical histo-pathological findings.

Calcium channel blockers are widely used in medical practice for the management of cardiovascular disorders. Gingival over growth is now a recognized unwanted effect associated with many of calcium channel blockers. Of this large group of drugs, the dihydropyridines are the agents most frequently implicated.[2]

Amlodipine a newer agent of dihydropyridine, used for treatment of hypertension and angina, was first reported for causing gingival overgrowth as side effect, by Seymour et al in 1994.[3]

Table 1. Drugs Causing Gingival Overgrowth[3,13]

Category	Pharmacologic agent
Anticonvulsants	Phenytoin Sodium valproate Phenobarbitone Vigabatrin Primidone Mephenytoin Ethotoin Ethosuximide Methosuxinimide
Immunosuppressants	Cyclosporin Tacrolimus Sirolimus
Calcium channel blockers	Nifedipine Nitrendipine Felodipine Nicardipine Manidipine Amlodipine Nimodipine Nisoldipine Verapamil Diltiazem

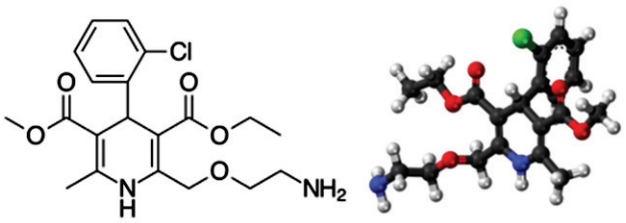

Figure 1. **Pharmacological Profile (Amlodipine)**

Long acting dihydropyridine (other members:-nifedipine, nicardipine, isradipine, nitrendipine & felodipine)

Mechanism of action: coronary and peripheral arterial vasodilatation

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[4]

CLINICAL & HISTOLOGICAL FEATURES

1. Clinical manifestation of gingival enlargement frequently appears within 1-3 months after initiation of treatment with the associated medications[5]
2. The growth starts as a painless, beadlike enlargement of the interdental papilla, and extends to the facial and lingual gingival margins. As the condition progresses, the marginal and papillary enlargements unite; they may develop into a massive tissue fold covering a considerable portion of the crowns[6]
3. When uncomplicated by inflammation; the lesion is mulberry-shaped, firm, pale pink, and resilient; with a minutely lobulated surface and no tendency to bleed. The enlargement characteristically appears to project from beneath the gingival margin, from which it is separated by a linear groove[7]
4. Presence of enlargement makes plaque control difficult, often resulting in a secondary inflammatory process that complicates the gingival overgrowth caused by the drug. Secondary inflammatory changes not only add to the size of the lesion caused by the drug, but also produce a red or bluish red discoloration, obliterate the lobulated surface demarcations, and increase bleeding tendency[8]
5. The enlargement is usually throughout the mouth,

but is more severe in the maxillary and mandibular anterior regions. It occurs in area in which teeth are present, not in edentulous spaces, and the enlargement disappears in areas from which teeth are extracted. Hyperplasia of the mucosa in edentulous mouths has been reported but is rare[9]

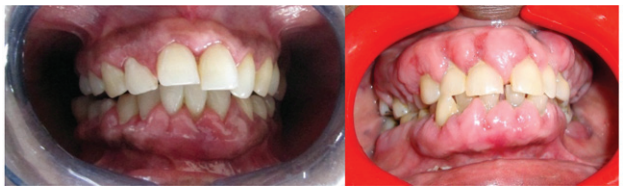

Figure 2. **It showing two cases of Amlodipine induced gingival enlargement reported to the Department of Periodontics, Government Dental College, Trivandrum**

Disfiguring gingival overgrowth triggered by this medication is not only aesthetically displeasing but often impairs nutrition and access for oral hygiene, resulting in an increased susceptibility to oral infection, caries, and periodontal diseases.[10]

Histologically, slight to moderate hyperkeratosis, thickening of the spinous layer, fibrosis of underlying connective tissue with fibroblastic proliferation, increase in the number of capillaries with slight chronic perivascular inflammation is seen. or substitution of medication. A pronounced hyperplasia of the connective tissue and epithelium. There is acanthosis of the epithelium, and elongated rete pegs extend deep into the connective tissue, which exhibits densely arranged collagen bundles with an increase in the number of fibroblasts and new blood vessels. An abundance of amorphous ground substance has also beenreported[11]

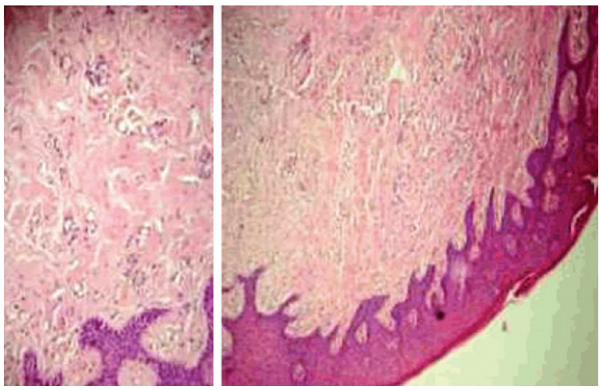

Figure 3. **It showing histopathology of a case of Amlodipine induced gingival enlargement**

Structural changes in the outer epithelial cell surface have been reported in cyclosporine-induced enlargements. The enlargement begins as a hyperplasia of the connective tissue core of the marginal gingiva and increases its proliferation and expansion beyond the crest of the gingival margin.[12] An inflammatory infiltrate may be found at the bottom of the sulcus, or pocket.

When this treatment approach is take as suggested by another case report, it may take from 1 to 8 weeks for resolution of gingival lesions.[12] Unfortunately, not all patients respond to this mode of treatment especially those with long standing gingival lesions.[13]

PATHOGENESIS

The pathogenesis of gingival overgrowth is uncertain and treatment is still largely limited to the maintenance of an improved level of oral hygiene and surgical removal of the overgrowth tissues. A number of factors affect the relationship between drug and gingival overgrowth.

ROLE OF FIBROBLASTS

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 showed 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

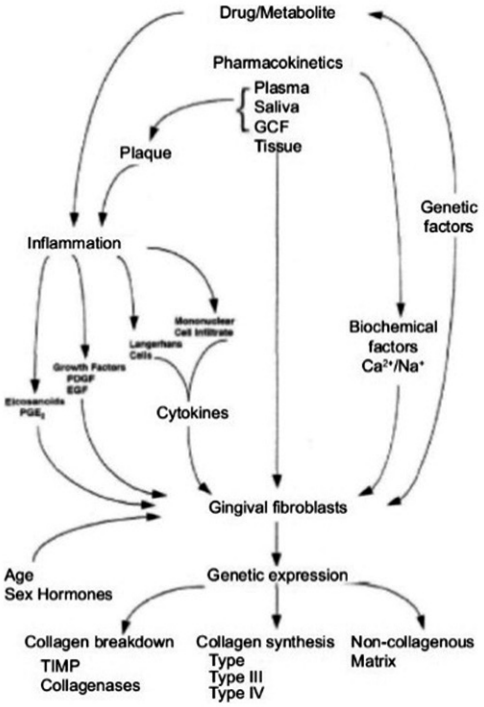

Figure 4. **Diagram explaining the pathogenesis[11]**

of fibroblast subsets in each individual which exhibit a fibrogenic response to this medication.[14,15]

ROLE OF INFLAMMATORY CYTOKINES

A synergistic enhancement of collagenous protein synthesis by human gingival fibroblasts was found when these cells were simultaneously exposed to nifedipine and interleukin-1b(IL-1b), a proinflammatory cytokine that tis elevated in inflamed gingival tissues.[16] In addition to IL-1b, IL-6 may play a role in the fibrogenic responses of the gingiva to thesemedications[17]

ROLE OF MATRIX METALLOPROTEINASE (MMP)

Because most types of pharmacological agents implicated in gingival enlargement have negative effects on calcium ion influx across cell membranes, it was postulated that such agents may interfere with the synthesis and function ofcollagenases[18] Kantarci et al.,[19]demonstrated that there are significantly higher numbers of basement membrane discontinuities in overgrowth tissues, sometimes containing epithelial-like cells. Disrupted basal membrane structure in gingival overgrowth tissues is accompanied by a discontinuous collagen type IV expression pattern and decreased laminin-5. These findings provided a new additional support for the hypothesis that epithelial plasticity and epithelial to mesenchymal transition promote gingival overgrowth, resulting in compromised basal membrane structure and increased interactions between epithelial and connective tissue layers that contribute to fibrotic pathology

Recently, Subramani et al.,[20] observed that mast cells participate in many inflammatory oral diseases, particularly those associated with fibrosis. They possess very diverse roles ranging from proinflammatory to immunomodulatory. Upon their activation, they promote the local renin angiotensin system generation consequently able to stimulate endothelin and other profibrotic mediators. Cyclosporin can modulate local expression of renin angiotensin system components such as angiotensinogen, angiotensin II and its receptors in gingival tissues, and gingival fibroblast cells.[21]

PREVENTION OF GINGIVAL ENLARGEMENT

In the susceptible patient, drug-associated gingival enlargement may be ameliorated, but not prevented by elimination of local factors, meticulous plaque control, and regular periodontal maintenance therapy. A 3-month interval for periodontal maintenance therapy has been recommended for patients taking drugs associated with gingival enlargement.[22]Each recall appointment should include detailed oral hygiene instruction and complete periodontal prophylaxis, with supra-and subgingival calculus removal as needed. In some instance orthodontic bands and/or appliances should be removed.[23]

DIFFERENTIAL DIAGNOSIS

A differential diagnosis requires thorough medical and dental histories, a careful evaluation of nature of enlargement, and an identification of the etiologic factors. A biopsy specimen may be required to confirm diagnosis.

Drug-induced gingival overgrowth must be differentiated from

1. **Inflammatory enlargement:** Acute inflammatory enlargement appears as a localized gingival swelling characterized by acute pain of rapid onset suggesting an abscess. Chronic inflammatory enlargement appears as deep red or bluish red, soft, friable with smooth, shiny surface along with bleeding tendency. Inflammatory enlargements usually are a secondary complication to any of the other types of enlargement, creating a combined gingival enlargement[24]
2. **Idiopathic or familial or hereditary gingival enlargement:** It affects the attached gingiva, as well as the gingival margin and interdental papillae. The facial and lingual surfaces of the mandible and maxilla are generally affected, but the involvement may be limited to either jaw. The enlarged gingiva is pink, firm, and almost leathery in consistency and has a characteristic minutely pebbled surface. Its cause is not known. However, some cases show a hereditary basis[25]
3. **Conditioned enlargement:** It occurs when the systemic condition of the patient exaggerates or distorts the usual gingival response to dental plaque. It includes hormonal (pregnancy, puberty), nutritional (associated with vitamin C deficiency), and allergic (plasma cell gingivitis). The gingiva shows features of chronic inflammatory enlargement especially interproximally. Plasma cell gingivitis consists of lesion located in the oral aspect of attached gingiva[26]
4. **Systemic diseases induced gingival enlargement:** Several systemic diseases viz. leukemia, sarcoidosis, tuberculosis, and other granulomatous

diseases can result in gingival enlargement. Hematological investigations (as in leukemia) and histopathological examination (leukemic infiltrate in leukemia, foreign body giant cell in sarcoidosis, tuberculosis) are useful in establishing the diagnosis[27]

5. **Neoplastic enlargement or gingival tumors:** It may appear as slowly growing spherical mass that tends to be firm and nodular or hard, wart-like protuberance from gingival surface
6. **False enlargement:** These are not true enlargements of the gingival tissues but appear as such. These result due to increase in size of the underlying osseous or dental tissues. The gingiva usually presents with no abnormal clinical features except the massive increase in size of area.

DIFFERENTIAL DIAGNOSIS AMONG DIFFERENT DRUGS

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[28]

In individuals, immunosuppressed with cyclosporin, 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. Other investigators have reported

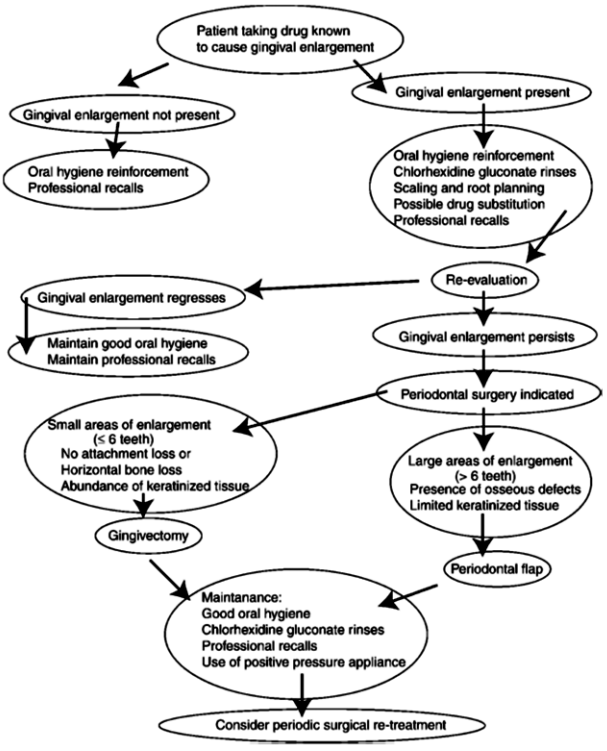

Figure 5. **Treatment Algorithm**[30]

that tissues affected by cyclosporin are generally more hyperemic and bleed more readily upon probing than tissues affected by phenytoin[29]

TREATMENT OPTIONS

The treatment of drug-induced gingival enlargement should be based on the medication being used and the clinical features of the case.

First, consideration should be given to the possibility of discontinuing the drug or changing the medication. These possibilities should be examined with the patient's physician. Simple discontinuation of the offending drug is usually not practical, but its substitution with another medication may be an option. If any drug substitution is attempted, it is important to allow for a 6- to 12-month period to elapse between discontinuation of the offending drug and the possible resolution of gingival enlargement before a decision to implement surgical treatment is made.

Alternative medications to the anticonvulsant phenytoin include carbamazepine and valproic acid, both of which have been reported to induce gingival enlargement to a lesser degree.

For patients who are taking nifedipine, which has a reported prevalence of gingival enlargement of up to 44%, other calcium channel blockers such as diltiazem or verapamil may be viable alternatives; their reported prevalences of inducing gingival enlargement are 20% and 4%, respectively. In addition, consideration may be given to the use of another class of antihypertensive medications rather than calcium channel blockers, because none of these drugs are known to induce gingival enlargement.

Drug substitutions for cyclosporine are more limited. Tacrolimus is another immunosuppressant that has been used with organ transplant recipients.[31] The incidence of gingival enlargement in patients receiving tacrolimus therapy is approximately 65% lower than that of individuals who are receiving cyclosporine-[32]Clinical trials have also shown that the substitution of cyclosporine with tacrolimus results in a significant decrease in the severity of gingival enlargement as compared with patients who are kept on cyclosporine therapy. In another study,[33] the same drug substitution resulted in a strong decrease in or the complete resolution of gingival enlargement in more than 70% of the patients who initially presented with cyclosporine-induced gingival enlargement. Therefore, the dental practitioner should consult with the treating

transplantation physician to investigate the possibility of a change in immunosuppressant therapy as one of the steps in the treatment of cyclosporine-induced gingival enlargement. Patients who take cyclosporine in combination with a calcium channel blocker tend to present an overall lower prevalence of and less severe gingival enlargement if the anti-hypertensive drug is amlodipine as compared with nifedipine[34]

The administration of the antibiotic Azithromycin has been shown to decrease the severity of gingival enlargement induced by the administration of cyclosporine. A 3-day course of systemic Azithromycin significantly decreased gingival enlargement, and the effect was observed as early as 7 to 30 days after the initiation of antibiotic therapy.[35] The use of Azithromycin to decrease cyclosporine-induced gingival enlargement resulted in significantly greater changes than those observed with an improvement in oral hygiene.[36] The topical administration of Azithromycin in the form of a toothpaste also decreased the severity of cyclosporine-induced gingival enlargement[37]

Second, the clinician should emphasize plaque control as the first step in the treatment of drug-induced gingival enlargement. Although the exact role played by bacterial plaque is not well understood, evidence suggests that good oral hygiene, chemotherapeutics[38]and the frequent professional removal of plaque decrease the degree of gingival enlargement and improve overall gingival health. The presence of drug-induced enlargement is associated with pseudo pocket formation, frequently with abundant plaque accumulation, which may lead to the development of periodontitis; meticulous plaque control therefore helps to maintain attachment levels. In addition, adequate plaque control may help to prevent the recurrence of gingival enlargement in surgically treated cases.

Third, in some patients, gingival enlargement persists after careful consideration of the previous approaches. These patients may require surgery, which may involve either gingivectomy or the periodontal flap.

Non-Surgical treatment: Professional debridement with scaling and root planning as needed has been to shown to offer some relief in gingival overgrowth patients.[39]

Surgical Periodontal treatment: Because the anterior labial gingival is frequently involved, surgery is commonly performed for esthetic reasons before any functional consequences are present. The classical surgical approach has been the external bevel gingivectomy. However a total or partial internal gingivectomy approach has been suggested as an alternative.[40]This more technically demanding approach has the benefit of limiting the large denuded connective tissue wound that result from the external gingivectomy, thereby minimizing postoperative pain and bleeding.

The use of carbon dioxide lasers has shown some utility for reducing gingival enlargement, an approach which provides rapid post operative hemostasis. Consultation with the patient's physician prior to surgical treatment regarding antibiotic and steroid coverage should take place in the immunosuppressed patient.

GINGIVECTOMY

Gingivectomy has the advantage of simplicity and quickness but presents the disadvantages of more postoperative discomfort and an increased chance of postoperative bleeding. It also sacrifices keratinized tissue and does not allow for osseous recontouring. The clinician's decision between the two surgical techniques available must consider the extension of the area to be operated, the presence of periodontitis and osseous defects, and the location of the base of the pockets in relation to the mucogingival junction.

In general, small areas (i.e., up to six teeth) of drug-induced gingival enlargement with no evidence of attachment loss (and therefore no anticipated need for osseous surgery) can be effectively treated with the gingivectomy technique. An important consideration is the amount of keratinized tissue present: remember that at least 3 mm in the apicocoronal direction should remain after the surgery is completed.

CONCLUSION

The use of medications with the potential to contribute to the development of gingival overgrowth is likely increase in the years to come. Among the old and relatively new pharmacologic agents involved in gingival enlargement, overall, phenytoin still has the highest prevalence rate (approximately 50%), with calcium channel blockers and Cyclosporine associated enlargements about half as prevalent. Current studies on the pathogenetic mechanism of drug associated enlargement are focusing on the direct and indirect effects of these drugs on gingival fibroblast metabolism. If possible, treatment is generally targeted on drug substitution and effective control of local inflammatory factors such as plaque and calculus. When these modalities fail to cause resolution of the enlargement, surgical intervention is recommended. These treatment

modalities, 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 novelin formation for the design of future preventative and therapeutic modalities. The treatment has also been extended to a wide arena with the introduction of innovative technologies.

END NOTE

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Conflict of Interest: None declared

Editorial Comment:

Gingival enlargement or hyperplasia is a phenomenon observed often with medium and long term administration of many drugs. The significance of this observation needs to be understood for various reasons. Our dental colleagues are better versed with this effect. This article, though not a clinical study, reviews the drugs that produce this adverse effect, the consequences and the measures needed to prevent and treat it.

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