Amlodipine Induced Gingival Hyperplasia

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ABSTRACT

Calcium channel blockers are one of the most commonly used drugs for the management of cardiovascular disorders and are known for causing gingival overgrowth as adverse effects. Now a day's, 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 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 hyperplasia.

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.

An increasing number of medications are associated with gingival enlargement. Currently, more than 20 prescription medications are associated with gingival enlargement.(1) 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 overgrowth 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)

Pharmacological Profile (Amlodipine)

- Long acting dihydropyridine (other members:- nifedipine, nicardipine, isoradipine, 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

Clinical manifestation of gingival enlargement frequently appears within 1 to 3 months after initiation of treatment with the associated medication.(5) Gingival overgrowth normally begins at the interdental papillae and is more frequently found in the anterior segment of the labial surfaces. (6) Gradually, gingival lobulations are formed that may appear inflamed or more fibrotic in nature, depending on the degree of local factor-induced inflammation. The fibrotic enlargement normally is confined to the attached gingival but may extend coronally and interfere with esthetics, mastication, or speech.(7) 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.(8)

Histologically, slight to moderate hyperkeratosis, thickening of the spinous layer, fibrosis of underlying connective tissue with fibroelastic proliferation, increase in the number of capillaries with slight chronic perivascular inflammation is seen.
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 of fibroblast subsets in each individual which exhibit a fibrogenic response to this medication.(9,10)

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 is elevated in inflamed gingival tissues. (11) In addition to IL-1b, IL-6 may play a role in the fibrogenic responses of the gingiva to these medications.(12)

Role of Matrix Metalloproteinase (MMP) Synthesis and Function.
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 of collagenases.(13)

Prevention and treatment of gingival enlargement
Prevention
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.(14) 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.(15)

Treatment
- **Drug Substitution/withdrawl**: The most effective treatment of drug-related gingival enlargement is withdrawal or substitution of medication. 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.(16)

Unfortunately, not all patients respond to this mode of treatment especially those with long standing standing gingival lesions.(7)

- **Non-Surgical treatment**: Professional debridement with scaling and root planning as needed has been shown to offer some relief in gingival overgrowth patients.(17)

- **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.(7) 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.(7)

Case Report
A 48 year old female was referred to the O.P.D. of Periodontia Department of National Dental College & Hospital, Dera Bassi. The patient complained of extensive gingival enlargement along with foul odor, bleeding and fetid discharge from gums. She also complained of continuous mild pain and a feeling of heaviness in both upper and lower jaws.

![Fig1: Preoperative photograph showing gingival enlargement](image-url)
On general examination, the patient was medium build; she was suffering from hypertension from 1 year and was under amlodipine therapy. E.C.G and blood investigations were performed and reported to be within normal limits. Lips were incompetent; hence patient had a mouth breathing problem.

Intraoral examination revealed that all teeth were present except left mandibular 2nd and 3rd molars. Left mandibular 1st molar and right mandibular 2nd and 3rd molars were carious. Cervical abrasion was present generalized on all teeth in oral cavity. A generalized nodular enlargement of the marginal and interdental gingiva on both facial and lingual aspect was noticed. In region of 12, 13 14 localized gingival enlargement was seen which was bright red in colour and fibrotic in consistency (Fig.1). At isolated places, particularly in anterior region, inflammatory changes were seen. Range of probing depth of gingival sulcus was recorded in between 3mm to 6mm. The examination of occlusion exhibited labioversion and diastamata of anterior teeth.

- **Radiographic examination:** Orthopantomographic examination revealed a generalized moderate horizontal bone loss.
- **Case Management:** Prior to local management, the patient was thoroughly assessed by a physician and a suitable premedication therapy was instituted. Under local anesthesia, the enlargement was resected segment wise by a modified flap surgical procedure. Restoration of carious teeth and replacement of missing teeth was performed. There were no postoperative complications and the healing was uneventful. The patient was followed up for a period of one year regularly. A marginal inflammatory recurrence, however, was noticed which could easily be managed by routine therapeutic procedures.

### Summary & Conclusions
The reported case is an example of slowly progressive periodontitis. This was superimposed by a combined type of gingival enlargement; basically a drug induced one, complicated by inflammatory changes due to plaque accumulation. Moreover, hormonal changes due to menopause appear to contribute further to the enlargement of gingival tissues.

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 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. Newer molecular approaches are needed to clearly establish the pathogenesis of gingival overgrowth and to provide novel information for the design of future preventative and therapeutic modalities.

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