Nonsurgical Management of Amlodipine Induced Gingival Enlargement – A Case Report

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Abstract Antihypertensive drugs in the calcium channel blocker group are extensively used in elderly patients. Gingival enlargement associated with Nifedipine was first reported in 1980's and is very rarely reported to be associated with Amlodipine and Felodipine. The mechanism through which these medications trigger a connective tissue response are still poorly understood. The most effective treatment of drug induced gingival overgrowth is withdrawal or substitution of medication combined with meticulous oral hygiene, plaque control, and removal of local irritants. When these measures fails to resolve the enlargement, surgical intervention is recommended. This case reports a rare case of Amlodipine induced gingival enlargement. The patient was successfully managed by drug substitution and nonsurgical periodontal therapy.

Keywords: Nonsurgical therapy, Amlodipine, Calcium channel blocker, drug induced gingival enlargement

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1. 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.

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 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].

2. 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].

3. 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 gingiva 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 fibroblastic proliferation, increase in the number of capillaries with slight chronic perivascular inflammation is seen.

4. 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 tis 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].

4.1. Role of Matrix Metalloproteinase (MMP)

4.1.1. 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].

5. 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].

5.1. Treatment

Drug Substitution/withdrawal: 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 gingival lesions [7].

Non-Surgical treatment: Professional debridement with scaling and root planning as needed has been to 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].

5.2. Case Report

A 60 year female patient visited to the dept. of periodontics with the chief complain of bead like enlargement, bleeding and painful gum since a month.

The bead like enlargement appeared first in the interdental papilla of maxillary and mandibular anterior teeth and gradually involves the facial and lingual aspect. Enlargement slowly increased in size and spread to the posterior areas. Patient also complained of bleeding from the gingiva while brushing, soreness and deep gnawing pain.

Her Medical history revealed that she was hypertensive, and on Amlodipine (5 mg twice daily) therapy since a year. Patient was not suffering from any other illness/drug allergy and she was not taking any other kind of medication.

On Intraoral examination, Generalized gingival enlargement with increased severity in maxillary arch and mandibular anterior region was note. Oral hygiene maintenance was poor. The enlarged gingiva was Erythematous, soft and edematous, and showed a lobulated surface with absence of stippling. There was generalized bleeding on probing. Heavy presence of calculus was also noted. Periodontal Examination revealed generalized moderately deep pocket. 31 and 41 were grade 3 mobile with severe bone loss and were indicated for extraction. No significant Radiographic changes were observed except for a moderate generalized bone loss.

The case was diagnosed as Generalized chronic periodontitis with drug induced gingival enlargement (Combined enlargement – *Inflammatory and Amlodipine induced.*). request was sent to physician for the drug substitution and consent was taken for the planned periodontal treatment. *Amlodipine was substituted with Losartan potassium* and chlorothiazide combination (50 mg, 12.5 mg once daily). Since the patient was not willing for extraction of 31, and 41 phase I therapy was initiated. Scaling, root planing & curettage was performed under L.A.Oral hygiene instructions were reinforced and was prescribed 0.2% chlorohexidine mouthwash twice daily and Patient was recalled after 15 days.

15 days after therapy

5.3. 15 Days after Phase I Therapy

On examination at the first follow up after nonsurgical periodontal therapy, patient had relief from soreness and painful gums. Intraoral examination revealed slight improvement in the condition of gingiva. The Intensity of erythema and bleeding on probing had subsided marginally. The degree of gingival enlargement was slightly reduced. Gingival curettage was repeated and oral hygiene instructions were reinforced.

Probing depth was more than 6 mm irt 11,12,13,14,15,21,22,23,24,25,32,33,43 and 44. Patient was recalled after 21 days, but patient, failed to follow the appointment, and she returned after a gap of 4 months.

5.4. 4 Months after Phase I Therapy

On examination, oral hygiene maintenance was good. **+Complete resolution of gingival enlargement was noted.** Pocket depth irt 11,12,13,14,21,22,23,24 had reduced. 13 showed a persistant mild gingival enlargement. Full mouth scaling and root planing was performed and curettage was repeated in 13.

6. 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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