Management of Drug Induced Gingival Overgrowth

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ABSTRACT:
Gingival enlargement is the overgrowth of the gingiva characterized by an expansion and accumulation of the connective tissue with occasional presence of increased number of cells. The most common forms of gingival enlargement are induced by systemic drugs, including the antiseizure drug phenytoin, the immunosuppressor cyclosporine, and nifedipine, the calcium channel-blocker with antihypertensive activity. Gingival enlargement can be managed locally and systemically with a combination of medical and dental treatment either surgically or non surgically. Co-operative teamwork and good communication between the patient, their doctor and their dentist are essential. Here we present two cases of drug induced gingival enlargement describing clinical features, pathogenesis, and diagnosis one managed by drug substitution and oral hygiene and other surgically.

Key words: Gingival enlargement, Gingivectomy, Drug substitution.

INTRODUCTION
Healthy gingiva is pale pink or pigmented in colour, and surrounds tightly around the neck of the tooth like a collar. Drug induced gingival enlargements are unwanted adverse effect of some drugs such as Cyclosporine, Phenytoin and calcium channel antagonists.¹ This can be a cosmetic problem, interfering with eating and speech, impede effective tooth cleaning or force the teeth out of alignment. Gingival enlargement can be managed locally and systemically with a combination of medical and dental treatment. Co-operative teamwork and good communication between the patient, their physician and the dentist is essential.² The management of gingival overgrowth seems to be directed at controlling gingival inflammation through good oral hygiene regimen. However, drug substitution or withdrawal is the most effective treatment modality where resolution of enlargement is seen within 1 to 8 weeks but, in longstanding cases surgical excision is the most preferred method of treatment, followed by rigorous oral hygiene procedures.³ This case report
describes the management of two drug induced gingival overgrowth one managed by drug substitution and other by surgical method.

**CASE -1**

A 43 years old female patient reported to Department of Dental surgery with a chief complaint of swollen gums and bleeding on brushing from last 2 weeks. On elaborating the history of presenting illness she noticed bleeding from the gums while brushing for the last 15 days and was not associated with pain and pus discharge. Patients past medical history revealed to be a diagnosed case of hypertension for which, the patient received Amlodipine 5mg/day single dose orally for last 6 months. The dose was increased recently to 10 mg/day by the patient's civil physician 2 months back due to high blood pressure. On intraoral examination showed generalised reddish “bead like” enlargement of interdental papillae and the consistency of which was soft and edematous with loss of stippling (Fig 1 A&B). The oral hygiene of the patient was poor with supragingival calculus deposits present with 3-5mm of periodontal pockets characterized more of pseudo pocket in nature. Based on the history and clinical examination a diagnosis of drug induced gingival enlargement was established.

Treatment plan was formulated, patient was first referred to medical specialist and cardiologist for opinion of drug substitution. Amlodipine 10mg was substituted with Enalapril 5mg once daily dose, later patient was taken up for phase I therapy where full mouth scaling and polishing was done oral hygiene instructions were given. Patient was motivated to follow meticulous plaque control and routine follow-up was done. Patient was taken up for periodontal flap surgery in lower anteriors which did not show any improvement after maintenance phase. Internal bevel gingivectomy was planned from 33 to 43 region under local anaesthesia (Fig 4). A mucoperiosteal flap was raised complete scaling and root planing was done to remove subgingival calculus and granulation tissues. Patient was re-evaluated after 1, 3 and 6 months and the periodontal parameters were compared to baseline. There was a significant improvement in periodontal health with decreased bleeding, reduction of enlargement and pocket depth (Fig 5).

**DISCUSSION**

Increase in size of the gingiva is a common feature of gingival diseases. The current accepted terminology for this condition is “gingival enlargement” or “gingival overgrowth”. This is strictly a clinical description of the condition and avoids the erroneous pathologic connotations of terms used in past such as “hypertrophic gingivitis” or “gingival hyperplasia”.4 Gingival enlargement may be caused by a multitude of causes. Bokenkamp in 19944 has given score for gingival enlargement as

- **Grade O** - No sign of gingival enlargement,
- **Grade I** - Enlargement confined to interdental papilla,
- **Grade II** - Involves papillae and marginal gingiva,
- **Grade III** - Enlargement covers ¾ or more of the crown.

Of the several drugs currently, more
than 20 drugs are associated with gingival enlargements\(^5\) and can be broadly divided into three categories-

1. Anticonvulsants (Phenytoin, Phenobarbital, lamotregine, valproate, vigabatrin, exthosuximide, topiramate and primidone.\(^6\)
2. Calcium channel blockers (Nifidipine, Amilodipine and Verapamil).\(^7\)
3. Immunosuppressive drugs like Cyclosporine A\(^2\)

Drug-induced gingival enlargement was first observed in patients who were taking phenytoin for epilepsy, with approximately 50% having gingival overgrowth. Cyclosporine is an immunosuppressant which has been reported to cause gingival enlargement in 25-80% of patients.\(^2\) The mechanism through which these medications trigger a connective tissue response in the gingiva is still poorly understood. Because only a subset of patients treated with these medications will develop gingival overgrowth, it has been hypothesized that these individuals have fibroblasts with an abnormal susceptibility to the drug and other reason is the nature of gingival which is considered to be foetal collagen type.\(^3\)

Drug-induced gingival enlargement consists of soft tissue growth that begins between the teeth and increases in all directions. As the tissue enlarges it develops a characteristically thickened and lobulated appearance. It may partially or completely cover the tooth surfaces, including the occlusal (chewing) surfaces, as well as extending the other way, into the sulcus.\(^4\) The epithelial surface is usually smooth and fibrotic, but can be nodular in cyclosporine-induced enlargement. If there is underlying periodontal disease then the tissues may be inflamed, red or purplish in colour, and highly vascularised, with a tendency to bleed profusely. Gingival enlargement tends to be more severe in areas where plaque accumulates, such as at the edges of fillings and around orthodontic appliances. It is rarely seen in edentulous areas.\(^3\) Gingival enlargement impedes effective plaque control and regularly traps plaque or food, producing halitosis or suppuration. There is a tendency for gingival enlargement to be distributed symmetrically and for the anterior teeth to be more severely affected than the posterior teeth. Clinical parameters such as the standard of oral hygiene, drug dosage, and serum and salivary levels have some relationship to the incidence of gingival enlargement. Generally, a higher dose and poorer plaque control or more plaque retentive sites are more likely to be associated with gingival enlargement. However, there is no direct relationship and these factors do not fully explain the incidence or the characteristics of the lesion.\(^5,6\)

The pathogenesis of drug-induced gingival overgrowths of a multifactorial nature and is affected by factors such as age, demographic variables, genetic predisposition, oral hygiene status, pharmacokinetic variables and molecular and cellular changes in gingival tissues. Cyclosporine, phenytoin and calcium-channel blockers can influence the metabolism of some age-dependent hormones (eg. testosterone) which could have a direct effect on gingival cells population.\(^7\)

Studies have also demonstrated that patients developing gingival enlargement have high frequency of particular HLA antigens and genetic markers (Cytochrome P450, HLA-DR2,) and this appears to be related to a genetic predisposition for this pathology and may also be due to mutation of alpha 2 beta 1 integrin on fibroblast or 807U/C gene or SOS -1 gene (son of sevenless -1).\(^8,9\) Furthermore, it has also been reported that patients who expressed genetic markers such as HLA-B37 or HLA-DR1, are afforded some degree of protection against gingival overgrowth.\(^5\) Changes in gingival contour seen in drug-induced gingival overgrowth may also be exacerbated by plaque-induced gingival inflammation, through a mechanism of mechanical and chemical chronic irritation. In addition to plaque control and medical management by drug substitution, periodontal surgical treatment and multidisciplinary dental care are key strategies in managing gingival enlargement. Mild gingival enlargement may only require local management as improvement in oral hygiene, together with professional cleaning of the teeth, can lead to
resolution of inflammation and reduction in gingival enlargement. Treatment planning becomes more complex where there is periodontitis and gingival enlargement that is a cosmetic or functional problem. Periodontitis can be treated using conventional clinical care, but the gingival enlargement may require changes to the medication regimen, periodontal surgery to remove excess tissue, or a combination of the two.

Several alternatives to phenytoin are available, but they may not be as well tolerated or they may not control seizures as well. Some patients can switch to a lower dose of phenytoin combined with another anticonvulsant. If a patient develops gingival enlargement as a result of taking a particular calcium antagonist, they will usually also develop it in response to other calcium antagonists. Alternative classes of antihypertensive medication may be suitable for patients who are being treated for hypertension. The dose of cyclosporine may be reduced in the course of medical treatment, and can also be reduced in some cases where patients are on a maintenance dose, with no adverse effects. Once the gingival enlargement is drawn to the treating physician's attention, it may be possible to maintain a patient on a lower dose. Changing from cyclosporine to tacrolimus can be considered if significant gingival enlargement recurs after excision.

Recent observations suggest that roxithromycin, a macrolide antibiotic, may have a therapeutic role in reducing cyclosporine-induced gingival overgrowth, owing to its inhibitory effect on transforming growth factor-beta production. Other treatment modalities are use of Carbon dioxide laser or argon-laser for surgical treatment of gingival overgrowth because of decreased surgical time and rapid post-operative haemostasis.

**SUMMARY AND CONCLUSION**

The use of medications with the potential to contribute to the development of gingival overgrowth is likely to 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. 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 preventive and therapeutic modalities.

**REFERENCE**

Fig. 1A & B - Gingival enlargement before drug substitution

Fig. 2A & B - Patient after drug substitution and phase I

Fig. 3 - Intra oral manifestation of Cyclosporine induced gingival enlargement

Fig. 4 - Internal bevel gingivectomy

Fig. 5 - Post treatment

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