

Gingival overgrowth and drug association

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ABSTRACT

Drugs used locally or systemically induce several micro- and macroscopic tissue alterations. However, nearly 20 drugs have been reported so far in the literature, having association with the gingival enlargement. Many systemic diseases have their limited therapeutic options and such drugs or their metabolites have adverse influence on different systems/organs, and one of such is, they initiate or accelerate the overgrowth of gingival tissue. The over increase in the size of gingiva may be to the extent that, teeth may be partially or completely covered. And the resultant "gummy smile" may result in esthetic insult of the sufferer. In the presence of bacterial inflammation in gingiva, many of these drugs enhance collagen production by fibroblast cells, and simultaneously retard collagen destruction and hence increase the bulk of gingival tissue. It is apparent that there is subpopulation of fibroblasts those are sensitive to these drugs. The exuberant growth of gingival tissue has great esthetic concern, which may require mechanical removal of bacterial plaque, calculus, and surgical intervention and/or substitution of drug therapy by analogs. Relatively healthy oral environment provided by the dentist will reduce local micro-flora that will help eliminating the major focus of infection. Patient's physicians, general practitioners and dentist need to make coordinated and concise treatment plane to prevent or minimize the overgrowth and will be beneficial for the patients. This article will facilitate full information to physicians and general practitioners to involve dentists in the multidisciplinary treatment plane for these patients.

Key words: Cyclosporine, calcium channel blockers, collagen, fibroblast, neuralgia, phenytoin

INTRODUCTION

It is well-understood and ubiquitously accepted that bacterial plaque is the chief etiologic factor that causes the alteration in the periodontal tissue environment by inflammatory and immune responses, while the systemic factors enhance and aggravate the underlying pathologic mechanism in the connective tissue of gingiva. Increase in the size of the gingival marginal tissue and deepening of gingival sulcus act as nidus for bacterial plaque, and impair appropriate oral hygiene, and yield increased inflammatory reaction, and overgrowth.

For the drug-related gingival enlargement the term "gingival hyperplasia" was used earlier. However, this term did not accurately reflect the histological composition of the pharmacological modified gingiva; hence the terms "gingival enlargement" or "gingival overgrowth" are now practiced. Potential risk factors for the drug-induced gingival overgrowth include, poor oral hygiene, periodontal disease, periodontal pocket depth, degree of microbial plaque accumulation, and duration and dose of the drug.

Among the drug-induced gingival enlargement, phenytoin (dilantin) gingival enlargement is the earliest and commonly reported. Literature is also available on gingival overgrowth secondary to therapy with several drugs like phenobarbitone, primidone, carbamazepine, sodium valproate, mephenytoin,^[1] contraceptives, cyclosporine A (CsA), calcium channel blockers, and many others. Several studies have shown interaction of phenytoin, cyclosporine, and nifedipine with epithelial keratinocytes, fibroblasts, and collagen, those can lead to an overgrowth of gingival tissue in susceptible individuals. Phenytoin has been shown to induce gingival overgrowth by its interaction with a subpopulation of sensitive fibroblasts. Cyclosporine affects the metabolic function of fibroblast (e.g., collagen synthesis and degradation); whereas, nifedipine potentiates the effect of cyclosporine, and reduces protein synthesis by fibroblasts. A review of existing literature reveals that a cofactor clearly is needed to induce gingival overgrowth. In fact, there are several observations suggesting a modulation of inflammatory processes.

The prevalence of phenytoin-induced gingival overgrowth is estimated at 15-50% in patients taking the medication. Whereas, prevalence by cyclosporine in the transplant recipient patients is 27%. The incidence of gingival enlargement has been reported as 10-20% in patients treated with calcium channel blockers in the general population. However, these numbers should be interpreted with caution and clinicians need to observe at the population represented within each particular study (i.e. young persons with epilepsy and recipients of transplants). There are

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other intrinsic risk factors including the susceptibility of some subpopulations of fibroblasts and keratinocytes to phenytoin, cyclosporine, and/or nifedipine, and the number of Langerhan's cells present in gingival epithelium. The latter appears to be related to the presence of dental plaque and inflammation. Extensively studied and documented are the following three drugs that have been commonly found associated with gingival overgrowth, are reviewed here with emphasis on pathogenesis.

PHENYTOIN (DILANTIN)-ASSOCIATED GINGIVAL OVERGROWTH

Phenytoin since its introduction in 1930s by Merrit and Putnam, is the drug of choice as anticonvulsant in the treatment of grand mal, temporal lobe, and psychomotor seizures.^[2] Verifying degree of gingival hyperplasia is one of the most common side effects of phenytoin therapy which was first described by Kimball in 1939.^[3] For more than 60 years literature is available on the association between gingival enlargement and phenytoin.^[4] The incidence of enlargement reported by several investigators ranging from 40 to 50% and has been found more in teenagers. In India, 57% of children aged 8-13 years, who were on monotherapy of phenytoin, developed gingival overgrowth, generally within 6 months of commencement of treatment. It is observed that after starting the phenytoin therapy within 2-3 months, clinical sings of gingival enlargement appears as thickening of papillary and marginal gingiva with progression of lesion forming lobules and clefts and eventually covering the crown of the teeth. Clinically gingiva becomes firm, pale pink, with slightly inflamed margins and lobulated or pebbled surface. Enlargement is profound in anterior region in contrast to posteriors and occur in teeth bearing area. Contrarily few cases have been documented in the edentulous areas. Increased gingival bulk may limit to maintain good oral hygiene and thereby increases accumulation of bacterial plaque and inflammation. Edema, redness, and gingival bleeding are the secondary manifestations [Figure 1].

Other anticonvulsant drugs which are prescribed include ethotoin, mephentoin, valproic acid, methasuximide, succinimides, etc., The drugs like valproic acid, carbamazepine, phenobarbitone have been found to influence gingival morphology, are commonly prescribed for the therapy, and hence have been extensively investigated and documented for their association with gingival enlargement.^[4-7] Vigabatrin a relatively newer antiepileptic drug has also been reported to cause gingival overgrowth.^[8] In a 34-year-old male patient having phenytoin gingival enlargement, squamous cell carcinoma in relation to maxillary molar roots has been reported, but its association of cause could not be established.^[9]

Pharmacopathogenesis

Major metabolite of phenytoin is 5-parahydroxyphenylhydratoin (5-PHPPH). Mechanism of phenytoin-induced gingival enlargement is not clearly understood, but has been hypothesized that probably increase in the gingival connective tissue occurs

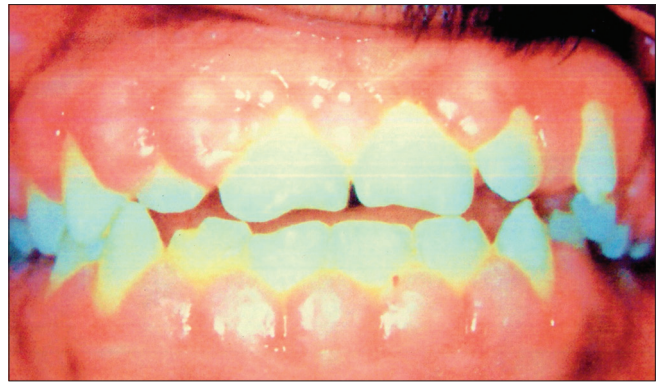


Figure 1: Phenytoin associated gingival overgrowth, pronounced enlargement in anterior teeth. Gingiva is firm, leathery and lobulated

due to proliferation of fibroblast cells and increased production of type-1 collagen.

Hassell *et al.*, have suggested that high activity fibroblasts become sensitive to phenytoin, and results in subsequent increased collagen production. Different subpopulation of the fibroblast cells in this kind of enlarged gingiva has been postulated.^[10] One of the subpopulation of fibroblasts may become sensitive to phenytoin in the presence of microbial plaque induced inflammation, resulting in increased synthesis of collagen.^[11] Also the enzyme collagenase secreted by phenytoin sensitive fibroblast is relatively inactive to degrade collagen. An imbalance in production and degradation results over accumulation of collagen and hence increase in the bulk of connective tissue. Changes in epidermal growth factor receptor (EGFR) density has also been reported as alternative mode of cause, due to direct effect of drug or its metabolites on folic acid metabolism, and adrenal function.^[12,13]

Management

Good oral hygiene and significant plaque control will reduce the gingival inflammation and help limiting further increase in gingival enlargement. Phenytoin gingival overgrowth is more confined on the anterior teeth and compromises the esthetics of the patient. Gingivectomy and gingivoplasty are the treatment of choice, followed by intensive oral hygiene home care program. Phenytoin is still a drug of choice for grand mal and psychomotor epilepsy and epileptic patients require regular medication, discontinuation or substitution may always not be possible. In a study conducted by Prasad *et al.*, concluded that systemic folic acid prescribed along with phenytoin delays the onset and reduces the incidence and severity of gingival overgrowth.^[14]

NIFEDIPINE-INDUCED GINGIVAL HYPERPLASIA

Calcium channel blockers are also called calcium antagonists and their use has been associated with gingival overgrowth. Nifedipine (calcium channel blocker) is extensively used for the treatment and prophylaxis of certain cardiovascular conditions

and is a known calcium antagonist who inhibits the influx of the calcium into the cardiac and smooth muscle cells. This results in a reduction in contractile process of cardiac muscle leading to a reduction of arterial blood pressure. Total number of prescriptions with the calcium channel blockers is increasing in recent years. Gingival enlargement associated with nifedipine was first reported in early 1980s.^[15] Gingival overgrowth has been reported in 1-10% of the patients on calcium channel blockers. Ramon *et al.*, 1984,^[16] and Shaftic *et al.*, 1986,^[17] reported prevalence of overgrowth as 0.5-83% for nifedipine and 74% for diltiazem; whereas, Miller and Damm (1992) have observed 4% enlargement with verapamil therapy.^[18] Some of the calcium channel blocker prescribed for different cardiovascular ailments are listed below and have been found to cause enlargement of gingiva.

- Nifedipine (Procardia)
- Diltiazem (Cardizem)
- Verapamil (Calan)
- Felodipine (Plendil)
- Amlodipine (Norvasc)
- Lacidipine and nitrendipine.

Nitrendipine an analogue of nifedipine has also been reported to induce gingival enlargement.^[19] Clinical features of nifedipine-associated gingival overgrowth are similar to those of phenytoin induced enlargement. Nifedipine gingival enlargement shows extensive inflammation that bleeds on slight provocation [Figure 2]. Gingival enlargement is one of the many side effects of this drug, other side effects though are rare include hypotension, peripheral edema, flushing, palpitation, headache, dizziness, nausea, tiredness, and syncope. These side effects usually occur at the beginning of the treatment and decreases as the treatment commences.

PHARMACOPATHOGENESIS

The possible hypothesis to explain this overgrowth is that the fibroblast contains strongly sulfated mucopolysaccharides those are ground substance precursors. After an interaction between nifedipine and gingival fibroblasts, overproduction of collagen and extracellular ground substance occur and lead to increase in the size of gingiva. The drug interferes with calcium metabolism of fibroblast cells and hence reduces the production of degrading enzyme collagenase. It has been suggested that there may be subpopulation of fibroblasts which are sensitive to nifedipine and causes increase in collagen production.^[20]

Management

Nifedipine gingival overgrowth decreases following the withdrawal of drug. Exacerbation occurs when the drug is reintroduced and decreases second time with withdrawal of the drug. The dosage of nifedipine has no correlation with gingival enlargement. Bacterial plaque control may lead to resolution of inflammation, but the enlargement does not completely regress. Excision of gingival overgrowth becomes mandatory to overcome esthetic concern.

CSA-ASSOCIATED GINGIVAL ENLARGEMENT

Cyclosporine, a potent immunosuppressant has been widely used since early 1980s in organ transplant recipients^[21] and treatment of psoriasis and other autoimmune disorders.

CsA causes gingival enlargement in 30% patients receiving the drug. Successful use of CsA in transplant medicine has been limited by development of prominent renal, cardiac, and gingival fibrosis.^[22] Several patients on CsA have been documented with gingival overgrowth. Renal and cardiac fibrosis may be so severe as to cause transplant failure.^[23] Pediatric heart-lung transplant recipients on CsA appear to be more susceptible to CsA-associated enlargement. Ninety-seven percent of these children have been reported to develop some degree of overgrowth.^[24] Significant role is played by T-lymphocytes in the graft (transplant) rejection. CsA by inhibiting the production and function of T helper lymphocyte cells (Th), suppress the immune response. At the same time B-lymphocyte cell system is unaffected by cyclosporine, allowing patient to maintain a humoral immune response to potential pathogens.^[22]

Other than CsA, basiliximab is also commonly used immunosuppressant drug, but has not been documented for gingival enlargement. Tacrolimus, an another analogue of CsA, has been documented to induce gingival overgrowth but this effect appears to be time related.^[25] The onset of cyclosporine-induced gingival enlargement is rapid and initial gingival changes may appear within 1-2 weeks of therapy. Children and adolescents have greater risk of developing gingival enlargement in comparison to adults. It has been observed that increase in gingival size and stabilization of growth may occur after few months of the therapy. CsA associated overgrowth is more hyperemic and bleeds more easily in contrast to phenytoin gingival overgrowth, but the clinical appearance of both is identical [Figure 3].

In the edentulous area, cyclosporine-associated enlargement has not been reported. In bone marrow transplant patients the incidence of gingival enlargement is 2% as compared to 81% in the renal transplant.

Varga and Tyldesley have reported a case of carcinoma arising in the cyclosporine associated gingival hyperplasia.^[26]

PHARMACOPATHOGENESIS

It is not understood whether poor oral hygiene is responsible for initial gingival inflammation and subsequently enhanced by CsA, or the drug initiates enlargement and facilitates accumulation of bacterial plaque, impairs oral hygiene, and precipitate inflammation.

Some studies on CsA-induced enlargement, found no correlation between oral dose of CsA and severity of gingival enlargement. Examination of tissue typing data in transplant recipient have



Figure 2: Nifedipine induced enlargement of upper and lower gingival

shown that HLA B37 positive patients are significantly more likely to show severe gingival enlargement, whereas the opposite is true for HLA DR1-positive patients.^[22] CsA-treated patients are often additionally prescribed prednisolone or azathioprine, those can modify the severity of gingival enlargement.^[25] It was found that CsA could react with a phenotypical distinct subpopulation of gingival fibroblast to enhance protein synthesis.^[27]

The histological appearance of the tissue shows an increase in the collagen fibers in the connective tissue of gingiva. The drug may reach the gingival connective tissue through blood stream and/or from the oral cavity through the crevicular epithelium. In the presence of inflammation the permeability of the sulcular epithelium increases, resulting in increased concentration of CsA in the connective tissue. The hypothesis is supported by the fact that CsA concentration is higher in whole saliva than in serum.

Management

There is no effective and predictable method of managing this condition. Complete resolution of gingival enlargement following reduction of dosage of CsA in one patient has been reported. Treatment may have optional drug therapy, for example, replacing cyclosporine to tacrolimus (an alternative immunosuppressant).^[28] Overgrowth can be minimized by bacterial plaque control measures. However, excess fibrotic tissue unresponsive to regress on withdrawal of the drug needs excision. Gingivectomy with carbon dioxide or yttrium aluminum garnet (YAG) laser is recommended for moderate to severe cases. CsA-induced hyperplasia is more hyperemic than phenytoin one; therefore it is necessary to control excessive bleeding during surgery. Recent observations suggests that roxithromycin a macrolide antibiotic may have a therapeutic role in reducing cyclosporine-induced gingival overgrowth, owing to its inhibitory action on transforming growth factor-beta production. Azithromycin in association with oral prophylaxis significantly reduces cyclosporine-induced gingival enlargement.



Figure 3: Cyclosporine associated gingival overgrowth. Gingiva is more fragile and bleeds on gentle provocation

DIFFERENTIAL DIAGNOSIS

Firm, leathery, fibrous enlargement of gingival tissue can also be associated with heredity, hormones, idiopathic, syndromes, and drug factors.

Hereditary Gingival enlargement has a definite family history and is an isolated abnormality. Gingival enlargement is inherited as an autosomal dominant trait, or rarely, as an autosomal recessive trait.^[29] There may be a spontaneous gene mutation, hence a negative family history alone cannot dismiss hereditary gingival enlargement from differential diagnosis completely. Oral pathologist prefer a term “hereditary gingival fibromatosis” (HGF) for this kind of enlargement. Other characteristic features of HGF are hypertrichosis, mental retardation, and coarse and thickened facial appearance simulating acromegaly.

In leukemic infiltration the gingival tissue often is purple-red with secondary inflammation. There is acute onset of hemorrhagic gingival oozing and consistency of gingiva is soft and fragile with dark red to purple color.

Tuberculosis and other granulomatous diseases including orofacial granulomatosis, Crohn’s disease, and sarcoidosis, can also mimic drug-induced gingival enlargement.

Gingival enlargement may have rare association with the following conditions

- Inclusive-cell disease (mucopolipidosis II).
- Acanthosis nigricans.
- Borrone di Rocco Crovatto syndrome.
- Cantu syndrome.
- Winchester syndrome.

DISCUSSION

The prevalence of gingival enlargement in healthy population has been estimated to be between 4.0 and 7.5%.^[1,2] Kimball (1939)

was among the first to report gingival overgrowth associated with phenytoin, reporting that 57% of patients taking this drug had gingival overgrowth.^[31] Phenytoin, nifedipine, cyclosporine, and other similar drugs mentioned above or analogue, despite of their therapeutic dose, are found to cause gingival enlargement. It has also been observed that nifedipine potentiates the adverse effect (i.e. gingival overgrowth) of cyclosporine. Morbidity can be severe in some cases because of gross overgrowth of gingival tissue, which can lead to gingival bleeding, pain, teeth displacement, and periodontal disease; but mortality has not been reported. Racial and gender predilection has not been found for drug-induced gingival overgrowth, although one study reported, males three times more likely than females to develop gingival overgrowth with calcium antagonists.^[30] Similarly no age predilection exists for the onset of drug-induced gingival overgrowth; however, phenytoin-induced gingival overgrowth appears to be more frequent in young patients with epilepsy. Most likely, this may be related to the age of the population, the nature of the disease, and poor oral hygiene. The probable explanation is that clinical and epidemiologic studies are primarily retrospective, and they are unable to fully clarify this association. The prevalence of phenytoin-induced gingival overgrowth is estimated at 15-50%, and for cyclosporine transplant recipient patients is 27%. Incidence of gingival hyperplasia has been reported as 10-20% in patients treated with calcium antagonists. However, these numbers should be interpreted with caution, and clinicians should look at the population represented within each particular study (i.e. young persons with epilepsy and recipients of transplants).

Fibroblasts are the predominant cells in the connective tissue of gingiva, the cell responsible for synthesis of fibers (collagen and elastin) and ground substance (proteoglycans and glycoprotein). However, collagenase is also produced by fibroblast to degrade old collagen and thus maintain the turnover of the collagen in the connective tissue. Fibroblast cells are calcium dependent for the production of collagen. These drugs interfere in the calcium transport and cause imbalance in the synthesis and degradation of the extracellular matrix by interfering with the synthesis and function of collagenase.

Although the pharmaceutical effect and primary target tissues of antiepileptic, immunosuppressant, antidepressant, and calcium channel blocker medication are different, but they act in similar way on gingival connective tissue, causing fibrous gingival enlargement. In cases involving gingival enlargement, gingival connective tissue does not necessarily exhibit an increased number of fibroblasts histologically.^[31,32] These findings indicate that at a molecular level, one etiologic factor of drug induced gingival enlargement may be the inhibition of collagen phagocytosis by means of reducing the expression of $\alpha 2\text{B1}$ integrin. Research suggests that integrin transducer conveys information from the extracellular matrix to the inside of the cell by triggering intracellular signaling pathways.^[33] These above stated drugs are

known to act as calcium antagonists. Intracellular calcium plays a significant role in the regulation of $\alpha 2\text{B1}$ integrin-mediated collagen phagocytosis by alternating integrin affinity.^[34]

Furthermore the actin-binding protein gelsolin is considered an important factor in gingival enlargement. Gelsolin contributes to maintain normal tissue integrity by regulating collagen phagocytosis through its integrin-binding affinity for collagen.^[33]

In orthodontic patients, gingival overgrowth has been suggested to be due to nickel accumulation in epithelial cells. Substitution of phenytoin with different anticonvulsant has long been suggested as the treatment of choice for the severely affected gingival enlargement. With the introduction of new generation of anticonvulsant drugs like lamotrigine, gabapentin, sulthiame, and topiramate, possibility of gingival enlargement can minimize. Changing the CsA to tacrolimus (an alternative immunosuppressive drug) may cause significant regression of gingival enlargement in renal transplant recipients.^[28]

All these drug-induced enlargements mentioned in the literature so far have clinical and histological characteristic similarity. Substantial evidence in the dental literature indicates that gingival enlargement can be controlled successfully, even under the continuous administration of calcium antagonists, by meticulous professional and individual oral hygiene, initiated prior to commencing therapy.

CONCLUSION

Several clinical studies concluded that in the relatively healthy oral cavity with optimal plaque control, the drug-associated gingival overgrowth is clinically unnoticeable. Drugs discussed here accentuates the overgrowth in preexisting gingival inflammation due to microbial plaque accumulation.

There are two concrete recommendations as protocol for the management of the drug-induced gingival overgrowth

1. Physician and dentist should make a coordinated treatment plane for the patients indicated for these drug therapy.
2. Established gingival overgrowth renders esthetic insult, which may be a primary concern and require intervention. Therefore, excision of the enlarged gingiva becomes an inevitable choice. All patients need to be helped to practice improved oral hygiene.

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