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Review Article

GINGIVAL ENLARGEMENT INDUCED BY ANTICONVULSANTS, CALCIUM CHANNEL BLOCKERS AND IMMUNOSUPPRESSANTS: A REVIEW

Bhardwaj Amit*, Bhardwaj Verma Shalu
SGT Dental College, Gurgaon, Haryana; Private dental practitioner, Gurgaon, India

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*Email: amitmds1980@rediffmail.com

ABSTRACT
Drug induced gingival enlargement is the term now used to describe medication related gingival hypertrophy or hyperplasia, a condition commonly induced by three main classes of drugs: anticonvulsants, antihypertensive calcium channel blockers and the immunosuppressant cyclosporine. The pathogenesis of drug-induced gingival enlargement is uncertain and there appears to be no unifying hypothesis that links together the three commonly implicated drugs. Various risk factors and etiologic agents like age, drug doses, genetic factors, plaque induced
inflammation etc have been proposed. Management of such condition when it interferes with aesthetic, function and occlusion includes non surgical and surgical intervention. It is important that the health practitioner is aware of the potential etiologic agents and characteristic features in order to be able to accurately diagnose and successfully manage such patients.

KEY WORDS: drugs, gingival enlargement, calcium channel blockers, phenytoin, cyclosporine.

INTRODUCTION

There is an ever increasing number of medications which may induce over growth of the gingiva, although a large range of pathological and idiopathic reactions can also result in gingival overgrowth. This review concentrates on the various over growths associated with pharmaceuticals, and their clinical management. The medication-induced gingival overgrowths occur as a side effect of drugs used mainly for non-dental treatment for which the gingival tissue is not the intended target organ.

'Overgrowth' is the preferred term for many of these medication - related conditions previously labelled as 'gingival hyperplasia' and 'gingival hypertrophy'. These terms do not truly reflect our current understanding of the macroscopically enlarged, histologically altered, gingiva.

Drugs associated with gingival overgrowth can be categorized broadly into three major groups according to their therapeutic actions, namely anticonvulsants, immunosupressants and calcium channel blockers

Although the pharmacologic effect of each of these drugs is different and directed toward various primary target tissues, all of them seem to act similarly on a secondary target tissue, i.e., the gingival connective tissue, causing common clinical and histopathological findings.

PREVALENCE

There is wide variation in the literature regarding prevalence of drug induced gingival hyperplasia. For phenytoin, the figure of 50% is quoted, whereas for cyclosporine and calcium channel blockers (CCBs) a much lower prevalence of 30% and 10% respectively is reported[1]. Among CCBs, prevalence of gingival hyperplasia is reported to be maximum for nifedipine (30-50%) treatment as compared to other CCBs[2]. Reported prevalence of gingival overgrowth (GO) after cyclosporine therapy varies between 8-81%. However, in a well controlled study, the overall prevalence was reported to be 21%[3]. Recent studies show that severity of GO is increased when patients taking cyclosporine in combination with CCBs[4]. Gingival hyperplasia is a rare condition. No population based or epidemiologic data is available in United States and Worldwide[5]. In India 57% of epileptic children aged 8-13 years who were undergoing phenytoin treatment, developed GO within 6 months of treatment[5]. Prevalence of phenytoin induced GO is estimated between 15-50 % in patients taking drug. Prevalence of GO in cyclosporine recipient transplant patients is 27 %. Incidence of GO has been reported as 10-20 % in patients treated with CCBs[5].

RISK FACTORS FOR DRUG INDUCED GINGIVAL OVERGROWTH

Age - Age has been considered an important risk factor for drug induced GO particularly for phenytoin and cyclosporine while age is not a risk factor for CCBs[1]. Phenytoin induced GO mainly observed in teenagers. Cyclosporine induced GO is more (52%) common in paediatric organ transplant patients as compared to adults[6.7].

Sex/ Race – After cyclosporine treatment, males were at greater risk from developing GO than females[7]. Males were shown to be 3 times more likely than females to develop GO when treated with CCBs[1]. Gender and race were not important risk factors for gingival changes to phenytoin[7]. No racial prediction exists for the onset of drug induced GO[5].

Drug variables – Doses, duration of treatment, serum and salivary concentrations remain controversial issue as far as gingival hyperplasia is concerned[7].

Drug combinations – There is evidence that combination of nifedipine and cyclosporine in organ transplant patients produces more GO than if each drug was used alone[8]. Incidence of this side effects was found to be higher when multiple anticonvulsants were taken together with phenytoin[7].

Periodontal variables – Plaque and gingival inflammation exacerbate drug induced GO. However, conflicting reports are available in case of cyclosporine induced GO. Plaque and gingival inflammation are also important risk factor for GO associated with CCBs.

Genetic factors- Cytochrome P-450 gene polymorphism which results in inter-individual variation in enzyme activity may be a risk factor for drug induced GO[7]. Genetic markers that have been investigated in relation to human lymphocyte

antigen (HLA) expression may be a risk factor involved in drug induced GO. Various forms of HLA eg. HLA-DR1, HLA-DR2, HLA-A19 and HLA-B37 have been identified but their exact role as risk factor is not completely understood[6,9].

TYPES OF PHARMACOLOGIC AGENTS

Anticonvulsants

Phenytoin remains the drug of choice for treatment for grand mal, temporal lobe, and psychomotor seizures since it was first introduced in the 1930s[10]. In the U.S., about 2 million patients take phenytoin for seizure control[11]. The first reported cases of phenytoin associated enlargement appeared more than 6 decades ago[10]. Since then, other anticonvulsant agents have been introduced that have frequently been linked to clinically significant forms of gingival enlargement. For example, gingival enlargement cases after chronic use of valproic acid, carbamazepine, or phenobarbitone in adult patients have been reported but are rare or have been poorly documented[12-14]. Vigabatrin is a relatively new antiepileptic agent that can cause gingival overgrowth[15]. However, there has been no systematic attempt to study gingival enlargement in patients taking vigabatrin.

Calcium Channel Blockers

Antihypertensive drugs in the calcium channel blocker group are used extensively in elderly patients who have angina or peripheral vascular disease[10,16]. The total number of annual prescriptions for this class of agents has continued to rise in recent years[10]. Gingival overgrowth associated with nifedipine was first reported in the early 1980s and was soon also described with diltiazem, verapamil, and in rare cases with amlodipine and felodipine

Immunosuppressants

Cyclosporin A (CsA) is a powerful immunosuppressant widely used for prevention of transplant rejection as well as for management of a number of autoimmune conditions such as rheumatoid arthritis[17,18]. Successful use of CsA in transplant medicine has been limited by the development of prominent renal, cardiac, and gingival fibrosis[19-22]. Renal and cardiac lesions may be so severe as to cause transplant failure[20-22]. Gingival lesions were reported as soon as results of the first clinical trials of this medication were published, and were more systematically examined in the 1980s.

Drugs commonly associated with gingival overgrowth, by category and Indian brand names are given in Table 1.

Table 1. Drugs commonly associated with gingival overgrowth

CATEGORY	DRUGS	BRAND NAMES
Anti-epileptics	Phenytoin	Dilantin, Eptoin
	Phenobarbitone	Gardinal, Phenetone
	Primidone	Mysoline
	Valproic acid	Valprid, Valtec, Valprin
Calcium Channel Blockers		
Dihydropyridines	Nifedipine	Adalat, Caligard,Depin
	Amlodipine	Amcard,Amdepin,Amlo
	Felodipine	Felogard,Penedil
	Nitrendipine	Nitrepin,Cardif
	Nicardipine	Nicapress-R, Cardene
	Verapamil	Calaptin,Vasoplan
Phenylalkylamine	Diltiazem	Dilzem,Dilgard,Angizem
Benzothiazepine	Bepridilhydrochloride	Bepricor
Immunosuppressant	Cyclosporine	Cyclomune, Graftin, Cyclophil
Miscellaneous	Erythromycin	Althrocin,Elucin
	Sertraline	Actiser,Daxid,Setalin

CLINICAL MANIFESTATIONS OF GINGIVAL ENLARGEMENT

Clinical manifestation of gingival enlargement frequently appears within 1 to 3 months after initiation of treatment with the associated medications[23]. Gingival overgrowth normally begins at the interdental papillae and is more frequently found in the anterior segment of the labial surfaces[10,16]. 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[10,16].

Disfiguring gingival overgrowth triggered by these medications is not only esthetically displeasing but often impairs nutrition and access for oral hygiene, resulting in an increased susceptibility to oral infection, caries, and periodontal diseases[18].

Most drug-associated gingival enlargements appear to be clinically indistinguishable, with the possible exceptions of phenobarbitone[14] and CsA[12]. In phenobarbitonetreated 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[14]. In individuals immunosuppressed with CsA, sometimes pebbly or papillary lesions appear on the surface of larger lobulations[24], which have been associated with the presence of *Candida* hyphae invading the gingival epithelium[24,25]. Other investigators have reported that tissues affected by CsA are generally more hyperemic and bleed more readily upon probing than tissues affected by phenytoin[12].

HISTOPATHOLOGY OF THE LESION

An ultrastructural study demonstrated that the increase in gingival tissue volume is primarily due to a connective tissue response rather than epithelial cell layer involvement[26]. The histopathology of the lesions in all drug categories is similar and is characterized by excessive accumulation of extracellular matrix proteins, such as collagen, or amorphous ground substance[10,11,16].

Varying degrees of inflammatory infiltrate exist, while an increase in the number of fibroblasts remains controversial[27-29]. The predominant type of infiltrating inflammatory cell is the plasma cell. Parakeratinized epithelium of variable thickness covers the connective tissue stroma, and epithelial ridges may penetrate deep into the connective tissue, creating irregularly arranged collagen fibers[26].

TREATMENT

Drug substitution

One of the foundations of treatment of all drug induced gingival overgrowths is drug substitution. Substitution of Phenytoin (PHT) with a different anticonvulsant drug has long been advocated as treatment of gingival overgrowth. The feasibility of drug substitution has increased in recent times with the addition a new generation of anticonvulsant drugs such as vigabatrin (Sabril), lomatrigine (Lamictal), gabapentin (Neurontin), sulthiame (Ospolot) and topiramate (Topamax). Reduction of gingival overgrowth after withdrawal of PHT has been reported[30] and complete regression after six months has been described in a small group of children[31]. Reduction in the dose of Cyclosporine (Cs) has been shown to be beneficial[32],however, the nature of organ transplants often means that alternative therapy or dose

reduction is not available. Some patients can use more conventional immunosuppressants such as steroids and azothioprine but survival rates are not as good. New immunosuppressants such as tacrolimus (FK506) (Prograf), rapamycin and mycophenolate mofetil (MMF) CellCept may offer some hope, as to date these have not been reported in association with gingival overgrowth. Withdrawal and substitution of the drug along with improved oral hygiene has been successful in many cases of nifedipine gingival overgrowth[33,34]. Unfortunately, not all cases respond to this treatment , particularly patients with long-standing overgrowth[35]. In a similar manner, drug substitution has been effective in some cases of gingival overgrowth due to verapamil[36], amlodipine[37] and felodipine[38]. It should be remembered that the conditions for which patients are taking these drugs can be very difficult to control and physicians may be very reluctant to modify an effective drug regime 'just for the gums'. Thus, while it is worth asking if drug substitution is possible, the dentist should understand that a negative response is not necessarily a disregard for the gingival problem, but rather a concern for the debilitating effects of the underlying condition.

Oral hygiene

Although the role of plaque has not been clearly defined in most medication-induced gingival overgrowth, there is no doubt that the resulting gingival inflammation can contribute an additional level of enlargement due to oedema, regardless of any initiating or contributing effect it may have on gingival overgrowth. Control of this inflammatory component of the gingival over growth , while important in itself, also aids in determining if surgical reduction is necessary and, additionally, allows for a less haemorrhagic field in any subsequent surgical intervention.

A programme of intense oral hygiene failed to prevent the onset of Cs-induced gingival over growth nor was it particularly effective at reducing existing overgrowth[39], but was of some benefit for general periodontal health,as expected. Chlorhexidine (0.12 per cent) mouthrinse has been reported to reverse recurrent Cs overgrowth following gingivectomy[40] and a study in rats indicates it may have a role in limiting but not preventing gingival overgrowth[41], however, the side effects of long-term chlorhexidine have to be considered. Pernu and others[42] have shown that gingival bleeding increases the relative risk of gingival overgrowth in patients taking Cs. Patients receiving nifedipine do not respond to conventional treatment as well as patients not taking the drug[43] . The role of plaque in nifedipine-induced gingival overgrowth is uncertain as no convincing longitudinal studies have investigated its role. It is difficult to draw conclusions regarding the role of plaque in verapamil gingival overgrowth. Two of the reported cases[44,45] had significant levels of plaque but many patients taking verapamil have high levels of plaque and no overgrowth. Good oral hygiene failed to reduce such overgrowth reported in children. Little information is available regarding plaque control and the other Calcium Channel Blockers (CCBs) but it is assumed that the situation would be similar to those mentioned.

Surgical treatment

The need for, and timing of, any surgical intervention needs to be carefully assessed. Surgery is normally performed for cosmetic/aesthetic needs before any functional need is manifested. In cases where drug therapy is likely to continue for many years , psychosocial considerations need to be considered in an effort to reduce the frequency and extent of any surgical intervention. While classical external bevel gingivectomy is still a viable treatment option, the large denuded connective tissue wound that results can be painful and requires careful postoperative care to prevent infection. There is a tendency towards the use of either a total or partial internal bevel gingivectomy approach. This technically more demanding approach has the benefit of allowing 'primary closure' thus reducing the chances of postoperative complications, however, it requires more time and skill to accomplish. Surgical treatment of PHT- , Cs- and CCB-induced gingival overgrowth has centred on gingivectomy by conventional methods and, more recently, the use of CO2 lasers[46,47]. The CO2 laser has been advocated because of the decreased surgical time, rapid postoperative haemostasis and the fact that often the underlying medical conditions are relative contraindications for conventional surgery.

Surgical excision has been tried in non-responding nifedipine cases[48] and it has been successful when combined with good oral hygiene[49]. Similar results have been found with verapamil[45], and diltiazem gingival overgrowth, although it does recur[50]. Most reports of amlodipine gingival overgrowth have also required surgical intervention . The only other reported case of felodipine gingival over growth received careful plaque control and surgical excision of the most prominent gingival tissue, however, the authors did not state how effective this therapy was[51].

CONCLUSION

Three types of pharmacologic agents, anticonvulsants, calcium channel blockers and immunosuppressants have been reported to cause gingival enlargement in susceptible individuals. The histologic response of the gingival connective tissue to these agents is uniformly characterized by an increase in the amount of collagen fibers as well as noncollagenous proteins. When all the evidence is considered, there appears to be three significant factors which are important in the expression of these gingival changes, notably drug variables, plaque – induced inflammatory changes in the gingival tissues and genetic factors which determine the heterogeneity of the fibroblast.

Prevention and treatment includes meticulous plaque control and frequent professional debridement. Furthermore, respective gingival procedures may be needed to improve function, aesthetics and access for home care. The periodontist is restricted in controlling gingival inflammation, correcting gingival contour and treating any pre-existing periodontal disease. Ideally, all patients about to be medicated with cyclosporine, phenytoin or a calcium channel blocker, should go through a full periodontal assessment and any disease present treated appropriately.

Physicians should be able to identify changes in the oral cavity related to the health of their patients. Unfortunately, most medical education curricula do not include sufficient information for the physician to appreciate oral biology and oral pathology. Thus, there is a great need for dental medicine and general medicine to work together in the care of drug induced gingival enlargement.

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