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Novel concepts in Drug Induced Gingival Overgrowth – A narrative review

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Abstract

Drug induced gingival overgrowth is a major side effect of certain drugs which are given for other non-dental reason which untentionally affects the gingival tissues. The major drug group causing enlargement is anticonvulsants, calcium channel blockers and immunosuppresants. This review article aims to focus on the type of drugs, the pathophysiology of drug induced gingival overgrowth with respect to both inflammatory and non-inflammatory mechanisms, risk factors associated with gingival overgrowth, clinical and histological features, differential diagnosis of the disease and the various treatment modalities and several recent concepts which involves molecular pathogenesis and gene targets for drug induced gingival enlargement.

Keywords: Drug induced gingival overgrowth, gingival enlargement, phenytoin, calcium channel blockers, immunosuppressive drugs.

Introduction

Gingival Overgrowth is defined as increase in the size of the gingiva either generalised or localised. Previously, the terminologies like Gingival hyperplasia, Gingival hypertrophy and Gingival Enlargement were used which was replaced by Gingival Overgrowth.[1] Gingival Enlargement can be classified based on their aetiology, location, extent or according to the distribution of the lesion. The aetiology of Gingival Enlargement can be of local factors like plaque and calculus, neoplasm, systemic factors like hormonal imbalance, drugs, blood dyscrasias, malnutrition, hereditary and genetic factors.[2]

Among the various types of Gingival Overgrowth, drug induced Gingival Overgrowth is more often occurs and it is mainly due to the side effect of certain drugs. Even though some medications which may induce overgrowth of the gingiva, there are range of pathological and

idiopathic reactions can also result in Gingival Overgrowth.

Drug Induced Gingival Overgrowth was first observed by Kimball et al in 1939 in patients taking Phenytoin as an anti-epileptic drug. Later immunosuppressants like Cyclosporine followed by anti-hypertensives mostly calcium channel blockers like Verapamil and Nifedipine causing DIGO were found. Other drugs like Erythromycin and oral contraceptives were also known to cause DIGO.[3]

The mechanism by which drugs causes Gingival Overgrowth is not certain. It may vary for each drug. Clinically, the Gingival Enlargement caused by the drug is indistinguishable. The main concern of Gingival Overgrowth is that it causes functional disturbances like difficulty in mastication, speech, altered tooth eruption, hinders plaque control and causes aesthetic concerns.[4]

The diagnosis of Gingival Overgrowth is based on the clinician's awareness of the aetiology of the condition through detailed history including medical and social information along with the clinical examination. A thorough medical history about the drugs being taken will give necessary information. The treatment modality of DIGO can be divided into two phases: the first, cause related therapy, involving attempts to modify etiological factors. The second phase of treatment is done when the first phase fails to eliminate interferences in speech, function or aesthetics. The surgical phase which is aimed to resect overgrown tissue (Gingivectomy), recontour the gingiva (gingivectomy) or both. Substitution of the drug and genetic level treatments also will play a major role in the future.[5]

Classification of Gingival Overgrowth

Gingival Overgrowth can be classified depends upon several factors which depends of aetiology, pathology, location and distribution.[6]

1.1. According to etiological factors and pathological factors:

1) Inflammatory enlargement
a) Chronic
b) Acute
2) Drug induced enlargement
a) Anticonvulsants (Phenytoin, Dilantin Sodium)
b) Immunosuppressants (Cyclosporine, Tacrolimus)
c) Calcium Channel Blockers (Nifedipine, Verapamil)
3) Enlargements associated with systemic disease or conditions
a) Conditioned enlargement
i) Pregnancy (Angiogranuloma/Epulis Gravidarium)
ii) Puberty
iii) Vitamin C deficiency (Scorbutic gingivitis)
iv) Plasma cell gingivitis
v) Non-specific conditioned enlargement (Pyogenic granuloma)
b) Systemic diseases causing enlargement
i) Leukemia
ii) Granulomatous disease
4) Neoplastic enlargement (gingival tumour)
a) Benign Tumours (Peripheral Giant Cell Granuloma)
b) Malignant Tumours (Angiosarcoma)
5) False enlargement

1.2. According To Location And Distribution:

1) Localized: Limited to the gingiva adjacent to a single tooth or group of teeth.
2) Generalized: Involving the gingiva throughout the mouth
3) Marginal: Confined to the marginal gingiva
4) Papillary: Confined to the interdental papilla
5) Diffuse: Involving the marginal and attached gingiva and papillae
6) Discrete: An isolated sessile or pedunculated, tumorlike enlargement.

Common Drugs Causing Gingival Enlargement

Anti Convulsants	Calcium Channel Blockers	Immuno Suppressants
Phenytoin	Nifedipine	Cyclosporine
Vigabartin	Nitrendipine	Tacrolimus
Phenobarbital	Amlodipine	Sirolimus
Ethosuximide	Felodipine	
Topiramate	Verapamil	
	Diltiazem	

Pathogenesis of drug induced gingival overgrowth

The administration of certain drugs can cause Gingival Enlargement. Although the incidence of drug-related Gingival Overgrowth has been established, the frequency of Gingival Overgrowth in the general population is unknown.[7] The pathogenesis of drug-induced Gingival Enlargement is poorly understood, although different mechanisms have been proposed.[8]

Molecular factors controlling collagen turnover in Gingival Overgrowth can act of two pathogenic pathways (Figure 1). One being accumulation of excessive synthesis and other being the inhibition of extracellular matrix breakdown.[9]

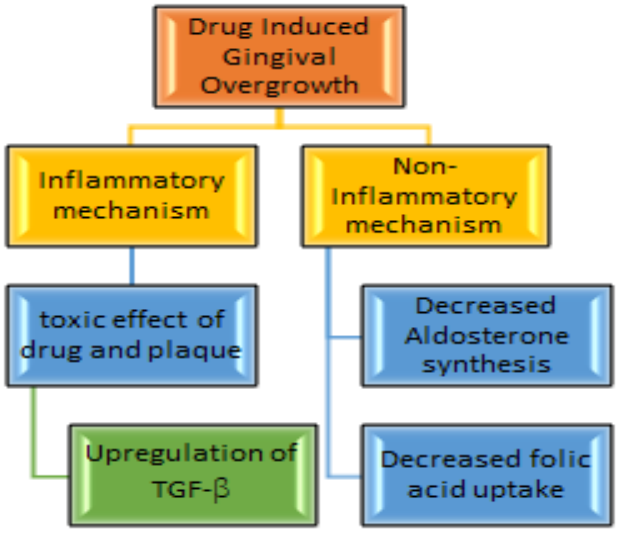

Figure 1: Mechanism of DIGO

The Pathogenesis of drug induced Gingival Enlargement may be due to:

Inflammation from the bacterial plaque

Considerable evidence supports the fact that plaque induced gingival inflammation exacerbates the expression of drug-induced Gingival Overgrowth. Most studies suggest that improving plaque control and the resultant reduction in inflammation will inhibit the development and recurrence of Gingival Overgrowth. It is said that inflammation secondary to dental plaque is a factor in pathogenesis of DIGO and plaque control should be utilized in both DIGO prevention and therapy.

Increased sulphated glycosaminoglycans

Increased tissue levels of sulphated glycosaminoglycans can occur with Phenytoin and Cyclosporin A exposure, possibly contributing to the occurrence of increased connective tissue matrix, that Gingival Overgrowth occurs due to overproduction of extracellular ground substance characterised by increased amount of mucopolysaccharides, collagen and active fibroblasts.

Role of Immunoglobulins

Phenytoin induces a significant decrease in serum IgA levels and an increase in both salivary IgA levels and the IgA secretion rate by the parotid gland. It also induces IgG and IgM production in Phenytoin induced gingival Overgrowth.

Gingival Fibroblast phenotype

Gingival Overgrowth was related to sensitivity of individuals to the drug or it's metabolites and they are classified as "responders" and "non-responders". Cyclosporin A and its major metabolite **OL-17** possibly reacts with a phenotypically distinct subpopulation of gingival fibroblasts, which causes an increase in protein synthesis and rate of cell proliferation.

Growth Factors (EGF, CTGF)

Nifedipine and Phenytoin tends to increase the synthesis of Epidermal Growth Factor, Transforming Growth Factor – Beta, basic Fibroblast Growth Factor and their receptors which in turn may be related to the Overgrowth of gingival tissues in drug induced hyperplasia.

Pharmacokinetics and tissue binding

There is probably a trough or minimal threshold dose below which Gingival Overgrowth does not occur. The usual therapeutic plasma level of Phenytoin necessary to maintain effective seizure control is **10-20** pg/ml. Patient compliance, metabolism and other medications are among the factors that may affect plasma levels and, thus, seizure control.

Collagenase activation

Nifedipine, Phenytoin and cyclosporin **A** may interfere with calcium transport and calcium-dependent processes. These drugs decrease the cytosolic calcium levels in gingival fibroblasts and T cells and interferes with T-cell proliferation or activation and collagen synthesis by gingival fibroblasts.

Disruption of fibroblast cellular Na+/Ca++ flux

Calcineurin permits Ca++-dependent inactivation of neuronal L-type Ca++ channels, and as excitation-driven entry of Ca++ through L-type voltage gated Ca++ channels controls gene expression in neurons, a variety of biochemical events are promoted resulting in a limitation of Ca++ entry.

Role of Folic acid

It is well established that Phenytoin may interfere with folic acid absorption and metabolism which primarily affects the epithelium, gonads and bone marrow. As a result of its role in DNA synthesis, tissues with higher turnover rates (such as epithelium) are often affected first.

Combination Hypothesis

Any of these factors may combine and play a major role in the pathogenesis of drug induced Gingival Overgrowth which contributes to the increased gingival mass.

Risk Factors

The identification of risk factors associated with both the prevalence and severity of drug-induced Gingival Overgrowth is important for all parties involved with this unwanted effect (Figure 2). Both Dentist and patient have an important role to play in improving oral hygiene and gingival health.[10] These factors can be identified under the following headings:

- Age and other demographic factors;
- Drug variables;
- Concomitant medication;
- Periodontal variables and
- Genetic factors.

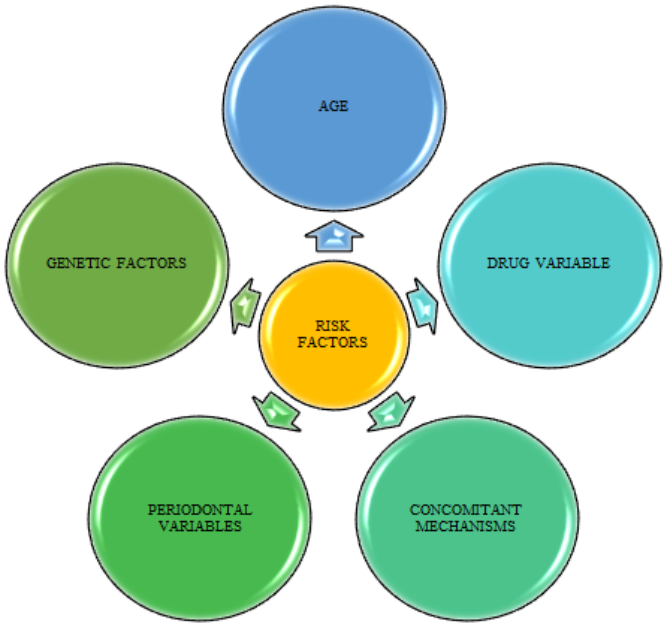

Figure 2: Risk factors for DIGO

Clinical features of drug induced gingival overgrowth

Initial enlargement of the interdental papillae, less frequently accompanied by the increased thickening of the marginal tissues (Figure 3). Affected tissues typically presents a granular or pebbly surface, with the enlarged

papillae extending facially and or lingually, obscuring the adjacent tissue and tooth surfaces. Affected papillae may become enlarged and leads to the formation of pseudoclefts.[11]

The tissue overgrowth diminishes once it reaches the mucogingival junction but the coronal progression of the overgrowth might partially or totally cover the crown of the teeth. Aesthetic disfigurement often results because The facial gingiva of the anterior sextants is more commonly affected. Gingival enlargement results in malpositioning of teeth and interference with normal masticatory function, speech and oral hygiene maintenance.

There are also reports of Phenytoin induced Gingival Overgrowth prior to the eruption of the primary teeth, which resulted in delayed eruption. Rarely Gingival Overgrowth was recorded in cases where edentulous patients and beneath pontics of fixed partial denture, and around each implant abutment. The surface of gingiva will be smooth and stippling may or may not be maintained. The enlarged tissues may be firm, fibrotic, non-tender and tenderness is usually due to secondary inflammation due to plaque accumulation at that site.[12]

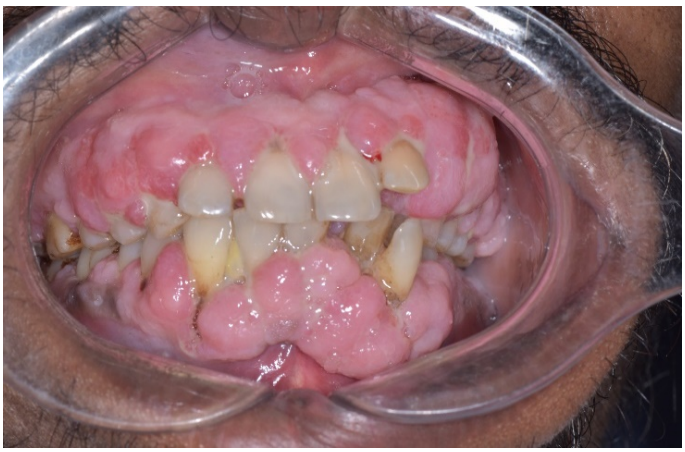

Figure 3: Phenytoin Induced Gingival Overgrowth

Histopathology of drug induced gingival overgrowth

Overlying irregular, multi-layered, para keratinized epithelium varying in thickness. Epithelial ridges penetrates the connective tissue and produces irregularly arranged collagen fibre bundles. The connective tissue is highly vascularized, and focal accumulations of infiltrating inflammatory cells have been seen. The predominant cell type in the inflammatory infiltrate is the plasma cell with lymphocytes seen to a lesser extent. Only T lymphocytes and monocytes are present adjacent to the junctional epithelium, with virtually no B lymphocytes.[13] Acanthosis and parakeratinization of the epithelium with pesudoepitheliomatous proliferation may be seen. Focal areas of myxomatous change have been seen more often in the immediate subepithelial tissues than in deeper areas. There is no evidence of increase in numerical density of fibroblast, which has led to the impression that Cyclosporin induced Gingival Enlargement is a result of an accumulation of non-collagenous material and thickening of the epithelium.

Ultra-structurally, there are some characteristics of active protein synthesis and secretion, with reduced cytotoxic or degenerative changes. Rarely myofibroblasts are also found. Basal and spinous layers of epithelium show distinct dilation of the intercellular spaces.[14]

Treatment of drug induced gingival overgrowth

Gingival Enlargement, regardless of its etiology, may be problematic and contribute to an increased risk for dental decay and periodontal disease. Gingival Overgrowth may decrease the efficacy of plaque control since enlarged gingival tissue often results in a periodontal pocket coronal to the cemento– enamel junction. The resulting pseudo-pocket represents overgrown gingival tissue rather than loss of periodontal attachment.[15]

Drug-induced Gingival Enlargement cases shows that the enlarged tissues have two components: a fibrotic, which is caused by the drug, and an inflammatory one is induced by bacterial plaque. These two components are always present in combination but the pathogenic process is

distinct for these both components. There are various treatment options for drug induced Gingival Enlargement which is broadly classified into:

- Non – Surgical approaches
- Surgical Approaches

Non-Surgical Approaches:

The main aim of non-surgical approaches is to minimize the inflammatory component in the gingival tissues and thereby avoid the need for surgery.[16]

They are:

- Oral Hygiene Maintenance
- Antiseptic Mouthwash
- Systemic Antibiotics
- Substitution Of The Drug

Surgical Approach:

When cause-related therapy did not bring adequate resolution of Gingival Overgrowth and interference with speech, function or aesthetics persists, surgery may be indicated. Recurrent and refractory cases are managed by periodontal surgical procedures to achieve more definitive results. Aesthetic concerns, such as enlarged gingiva that hides the natural shape and contour of the clinical crown, may be an indication for surgical treatment.

Basic surgical approach towards the gingival overgrowth is

- Gingivoplasty
- Gingivectomy
- Both

These procedures can be done manually using surgical blade, electrocautery or with Lasers. The aim is to resect overgrown tissue (gingivectomy), recontour the gingivae (gingivoplasty) or both. Removal of tissue also facilitates histological examination and diagnosis. In severe cases, surgery is indicated so that significant changes to gingival contour can be made to ensure the level of plaque control and optimum resolution. Gross resection of the soft tissues helps the patient in achieving optimum oral hygiene.[17]

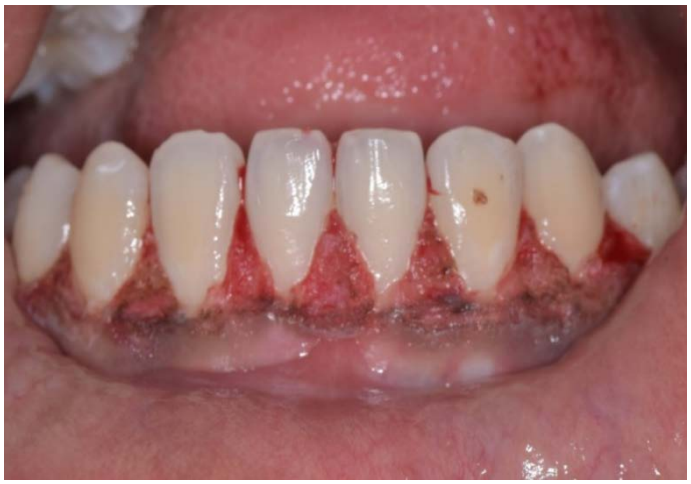

Figure 4: Laser Gingivectomy

Complications might arise due to various social factors and health concerns such as manual dexterity and learning difficulties. Even if complete resolution is unlikely without surgery, cause-related therapy should be attempted in the first instance to reduce inflammation and risk of recurrence post-operatively. Inflammation may lead to increased haemorrhaging at the time of surgery, compromising visibility and also inflamed tissues are more friable and difficult to handle which lead to increased surgical trauma, delayed healing and scarring.

Recent Advances

It has been showed that Nifedipine additively exaggerates IL-I beta induced canonical NF-KB nuclear translocation. Both p50 and Rela protein levels in the total lysate and nuclear fraction increased. It also implied that pro inflammatory cytokines may aggravate Gingival Overgrowth through NF-KB pathway and regulated downstream collagen synthesis. **Bortezomib, a proteasome inhibitor** mainly reversibly inhibits chymotrypsin like activity at the proteasome subunit and has an anti-inflammatory effect through blockade of NF-KB activation, suppression of T cells ad natural killer cells and downregulation of T cell related cytokines.

Proteasome inhibitors may suppress IL-1B degradation and attenuate IL-1B/Nifedipine-induced IKK–IL-1B–NF-KB–collagen activity.[18]

Phenytoin is known to inhibit FOXO-1 it reduces anabolic metabolism, increases apoptosis and arrests the cell cycle. FOXO-1 increases the production of TGF-β and contributes to Gingival Overgrowth. Decreased cellular folic acid leads to reduced expression of E-cadherin and SMAD (SMAD proteins are signal transducers and transcriptional modulators that mediate multiple signalling pathways) which reduces the expression of the AP-1 gene. Reduced AP-1 activates the TIMP-1 gene expression. The result is that Phenytoin decreases the MMP-1 by increasing the expression of TIMP-1. As a result of this, collagen accumulates in ECM and causes Gingival Overgrowth.[19]

It was reported that Marijuana consumption also resulted in Gingival Overgrowth. In his case report, a 34yr old patient reported with Gingival Overgrowth who had no history of any systemic medication and had habit of taking marijuana for almost 2 years in the wake of which the enlargement assisted by the frequency of consumption. The enlargement was generalised, diffuse, nodular and pebbled. The histological examination was same as that of drug induced Gingival Overgrowth with predominant connective tissue element. The mechanism suggested was that it was similar to Phenytoin causing same type of enlargement.[20]

Some authors analysed the gene expression profile of 12 genes that belong to the "Extracellular Matrix and Adhesion Molecules" pathway for amlodipine induced Gingival Overgrowth. Most of the significant genes were up-regulated. (CTNND2, COL4A1, ITGA2, ITGA7, MMP10, MMP11, MMP12, MMP26), except for COL7A1, LAMB1, MMP8, and MMP16, which were down-regulated. These proteins preferentially induce extra cellular matrix deposition. This study demonstrated that, in human gingival fibroblasts that were cultivated in vitro, amlodipine could promote the activities of genes belonging to the "fibroblast matrix and receptors".[21]

Conclusion

Ideally, all patients about to be medicated with cyclosporin, Phenytoin or a calcium channel blocker, should go through a full periodontal assessment and any disease presented treated appropriately. Unfortunately, for many of these patients this is impractical and such patients often present to the Dentist or Periodontist with existing Gingival Overgrowth. For many patients, surgical removal is the main option and the scalpel gingivectomy is still the best treatment of choice. Preventing recurrence of Overgrowth is a significant challenge to the Periodontist and members of the dental team. Change in medication is an option, but there may be medical or financial reasons why this cannot be expedited. Interdisciplinary approach in the management of such patients helps them by restoring the esthetics, phonetics, and mastication. Specialist input may ultimately be required to manage these patients. However, the General Dental Practitioner, Periodontist, and a Medical Practitioner combination is mandatory to render the functional and aesthetically desirable outcomes of the patient.

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