Drug Induced Gingival Enlargement

Contents

Introduction

- Increase in size of the gingiva is a common feature of gingival disease
- It is known as gingival enlargement
- 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 (**Academy Report, J Periodontol 2004**)

Classification

- Classified according to **Etiologic Factors & Pathologic Changes** as follows: (**Carranza 9 & 10th Ed.**)

I. Inflammatory Enlargement

A. Chronic
B. Acute

II. Drug-induced enlargement

III. Enlargements Associated With Systemic Diseases

A. Conditioned Enlargement

1. Pregnancy

2. Puberty

3. Vitamin C Deficiency

4. Plasma Cell Gingivitis

5. Nonspecific Conditioned Enlargement

B. Systemic Diseases Causing Gingival Enlargement

1. Leukemia

2. Granulomatous diseases

IV. Neoplastic Enlargement

A. Benign tumors

B. Malignant tumors

V. False Enlargement

- **According to Location & Distribution**

Localized: Limited to the gingiva adjacent to a tooth or group of teeth

Generalized: Involving the gingiva throughout the mouth

Marginal: Confined to the marginal gingiva

Papillary: Confined to the interdental papilla

Diffuse: Involving the marginal and attached gingivae and papillae

Discrete: An isolated sessile or pedunculatedtumorlike enlargement

- **The degree of gingival enlargement (Duckworth et al, 1966) are:-**

Grade 0: No signs of gingival enlargement

Grade I: Enlargement confined to interdental papilla

Grade II: Enlargement involves papilla and marginal gingiva

Grade III: Enlargement covers three quarters or more of the crown

- **Eva Ingles et al** (**Quintessence Int, 1999**)proposed specific criteria for the **Clinical Index For Drug Induced Gingival Overgrowth**:-

- **Grade 0**

  No overgrowth; firm adaptation of the attached gingiva to the underlying alveolar bone.

  There is slight stippling; there is no granular appearance or a slightly granular appearance.

  A knife-edged papilla is present toward the occlusal surface.

  There is no increase in density or size of the gingiva

- **Grade 1**

  Early overgrowth, as evidenced by an increase in density of the gingiva with marked stippling & granular appearance.

  The tip of the papilla is rounded.

  The probing depth is less than or equal to 3 mm.

- **Grade 2**

  Moderate overgrowth, manifested by an increase in the size of the papilla and/or rolled gingival margins.

  The contour of the gingival margin is concave or straight.

  Gingival enlargement has a buccolingual dimension of up to 2 mm, measured from the tip of the papilla

  The probing depth is equal to or less than 6 mm.

  The papilla is somewhat retractable.

- **Grade 3**

  Marked overgrowth, represented by encroachment of the gingiva onto the clinical crown.

  The contour of the gingival margin is convex.

Gingival enlargement has a buccolingual dimension of approximately 3 mm or more, measured from the tip of the papilla

The probing depth is greater than 6 mm.

The papilla is clearly retractable

- **Grade 4**

  Severe overgrowth, characterized by a profound thickening of the gingiva.

  A large percentage of the clinical crown is covered.

- According to **Academy Report** (**J Periodontol 2004**), drugs associated with gingival enlargement can be broadly divided into three categories:-

  1) Anticonvulsants

  2) Calcium Channel Blockers

  3) Immunosuppressants

Estimated Prevalence of Drug-Associated Gingival Enlargement According to the Most Frequently Reported Prevalence Rates(Academy Report, J Periodontol 2004)

Category	Pharmacologic Agent	Trade Name	Prevalence
Anticonvulsants	Phenytoin	Dilantin	50%[6,17,23]
	Sodium valproate (valproic acid)	Depakene, Depacon, Epilim, Valpro	Rare[3,5,23]
	Phenobarbitone	Phenobarbital, Donnatal	<5%[7]
	Vigabatrin	Sabril	Rare[8]
	Carbamazepine	Tegretol	None reported
Immunosuppressants	Cyclosporin	Neoral, Sandimmune	Adults 25- 30%[13,21,24] Children >70%[22]
Calcium channel blockers	Nifedipine	Adalat, Nifecard,	6-15%[18-20]

		Procardia,Tenif	
	Isradipine	DynaCirc	None reported
	Felodipine	Agon, Felodur, Lexxel, Plendil	Rare[3,20]
	Amlodipine	Lotrel, Norvasc	Rare[3,20]
	Verapamil	Calan, Covera, Isoptin, Tarka,Verelan	<5%[25]
	Diltiazem	Cardizem, Dilacor, Diltiamax,Tiazac	5-20%[26]

Risk Factors **(Academy Report, J Periodontol, 2004)**

Plaque

The severity of gingival enlargement in patients taking Anticonvulsants, Calcium Channel Blockers & Immunosuppressants correlates well with poor plaque control

Hence, recognized in the most recent classification system for periodontal diseases **(Armitage GC, Ann Periodontol 1999)** as Plaque- Induced Gingival Diseases Modified By Medications

Gender

Males are three times as likely to develop overgrowth (**Ellis JS et al, 1999**)

Age

Is inversely correlated (**Nakou M et al, 1998**)

Medication Interaction

Patients on Cyclosporine A who are also receiving a calcium channel blocker present with a greater severity of the gingival lesions than patients medicated with Cyclosporine A alone (**Thomason JM, 1997**)

Prevalence of gingival overgrowth in renal transplant recipients maintained on CsA& Amlodipine is higher than those receiving CsA&Nifedipine (**James JA et al, 2000**)

Genetic Susceptibility

In transplant recipients, **HLA B37**-positive patients are significantly more likely to show severe gingival enlargement, whereas the opposite is true about **HLA DR1**-positive patients (**Cebeci I et al, 1996**)

There is evidence that those patients who express **HLA-DR2** may be more susceptible to development of drug-induced gingival overgrowth (**Pernu HE et al, 1994**)

Pathogenesis (**International Scholarly Research Network, 2011**)

- The pathogenesis of drug-induced gingival overgrowths is still not completely understood.
- Collagen fibers are degraded by two pathways: The **Extracellular** one, which occurs by **Secretion Of Collagenases**; & The **Intracellular** one, by **Collagen Phagocytosis By Fibroblasts** [**M. Ogino et al, 2005**].
- In this regard, a common property of the 3 main classes of drugs that induce Gingival Overgrowth- Antiepileptic Agents, Immunosuppressants& Calcium Channel Blockers- is that they affect calcium metabolism.
- These drugs induce a decrease in the Ca^{2+} cell influx leading to a reduction in the uptake of **Folic Acid**, thus limiting the production of active collagenase.

⦿ **Role of Fibroblasts** (**Academy Report, J Periodontol, 2004**)

- It is hypothesized that individuals with fibroblasts that has an abnormal susceptibility to the drug develop gingival enlargement.

- 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 these medications (**Sinha-Morton R, Dongari-Bagtzoglou AI, 1999**)

⦿ **Role of Inflammatory Cytokines** (**Academy Report, J Periodontol, 2004**)

- A synergistic enhancement of collagenous protein synthesis by human gingival fibroblasts is present when exposed to Interleukin-1β (IL-1β), a pro-inflammatory cytokine that is elevated in inflamed gingival tissues & medications (**Johnson RB et al, 2000**)
- IL-6 may also play a role in the fibrogenic responses of the gingiva to these medications (**Williamson MS, 1994**)
- IL-6 appears to target connective tissue cells such as fibroblasts both by enhancing proliferation (**Fries KM et al, 1994**) and by exerting a positive regulation on collagen and glycosaminoglycan synthesis (**Duncan MR, Berman B, 1991**)

⦿ **Role of Matrix Metalloproteinase** (**Academy Report, J Periodontol, 2004**)

- MMPs interfere with the synthesis and function of collagenases (**Hassell TM, 1982**)
- Reduced levels of MMPs may contribute to the accumulation of extracellular matrix components (**Bolzani G et al, 2000**)

Histopathology (**Carranza & Academy Report, J Periodontol, 2004**)

- Increase in gingival tissue volume is primarily due to a connective tissue response rather than epithelial cell layer involvement (**Mariani G et al, 1993**)
- 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 (**Dongari AI et al, 1993, Hallmon WW &Rossmann JA, 1999**) & varying degrees of inflammatory infiltrate exist.

- 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 which exhibits densely arranged collagen bundles with an increase in number of fibroblast & new blood vessels
- Enlargement begins as hyperplasia of connective tissue core of marginal gingiva & ultimately expands beyond gingival margin
- Oxytalan fibres are numerous beneath epithelium & in areas of inflammation (**Baratieri A, 1967**) which are common along sulcular surface of gingiva

Clinical Manifestations

- Clinical features of the enlargements caused by the different drugs are similar (**Seymour RA et al, 1996**)
- Clinical manifestation of gingival enlargement frequently appears within **1 to 3 months** after initiation of treatment with the associated medications (**Meraw SJ, Sheridan PJ, 1998**)
- It is esthetically displeasing & often impairs nutrition and access for oral hygiene, resulting in an increased susceptibility to oral infection, caries & periodontal diseases (**Hassell TM, Hefti AF, 1991**)
- The growth starts as a painless, beadlike enlargement of the interdental papilla and extends to the facial and lingual gingival margins
- As the condition progresses, the marginal and papillary enlargements unite; they may develop into a massive tissue fold covering a considerable portion of the crowns, and they may interfere with occlusion
- When uncomplicated by inflammation, the lesion is mulberry shaped, firm, pale pink & resilient, with a minutely lobulated surface & no tendency to bleed

  The enlargement characteristically appears to project from beneath the gingival margin, from which it is separated by a linear groove.

- The enlargement is usually generalized throughout the mouth but is more severe in the **Maxillary & Mandibular Anterior Labial** surfaces (**Hallmon WW, Rossmann JA, 1999**)
- It occurs in areas in which teeth are present, not in edentulous spaces, & the enlargement disappears in areas from which teeth are extracted
- Hyperplasia of the mucosa in edentulous mouths is rare (**Dreyer WP, Thomas CJ, 1978**)
- Presence of enlargement makes plaque control difficult resulting in secondary inflammatory process that complicates gingival overgrowth
- Secondary inflammatory changes add to the size of the lesion caused by the drug & produce a red or bluish-red discoloration, obliterate the lobulated surface demarcations &result in an increased bleeding
- Oral hygiene by toothbrushing (**Elzay RP & Swenson HM, 1964**) or the use of chlorhexidine toothpaste (**Russell BJ & Bay LM, 1978**) reduces the inflammation but does not lessen or prevent the overgrowth
- The enlargement is chronic and slowly increases in size & when surgically removed, it recurs.
- Spontaneous disappearance occurs within a few months after discontinuation of the drug
- Characteristics Of Drug Induced Gingival Enlargement (**Mariotti, 1999**)
  - Variation in intrapatient&interpatient pattern
  - Predilection for anterior gingiva
  - Higher prevalence in children
  - Onset within 3 months
  - Change in gingival contour leading to modification of gingival size
    - Enlargement first observed at the interdental papilla
    - Change in gingival contour
    - Increase in gingival exudate
    - Bleeding on provocation
    - Found in gingiva with or without bone loss but is not associated with attachment loss
    - Profound inflammatory response of gingiva in relation to the plaque present

- Reduction in dental plaque can limit severity of lesion
- Must be using phenytoin, cyclosporine A or certain calcium channel blockers; the plasma concentration to induce the lesion have not been clearly defined in humans.

Anticonvulsants

- The first drug-induced gingival enlargements reported were those produced by **Phenytoin**
- Its relationship with gingival enlargement was reported in **1941** (**Glickman I, Lewitus M, 1941**)
- Other hydantoins known to induce gingival enlargement are Ethotoin (Paganone) &Mephenytoin (Mesantoin). {**Hallmon WW &Rossmann JA, 1999**}
- Other anticonvulsants that have the same side effect are the succinimides like Ethosuximide [Zerontin], Methsuxinimide [Celontin]) &Valproic Acid (Depakene) {**Hallmon WW &Rossmann JA, 1999**}
- Gingival enlargement occurs in about 50% of patients receiving the drug (**Seymour RA, 1996**)
- It occurs more often in younger patients (**Babcock JR, 1965**)
- There is a relation between the drug dosage & the degree of gingival overgrowth (**Kapur RN et al, 1973**)
- Although rare, phenytoin gingival overgrowth has also been observed in edentulous patients and beneath pontics of fixed partial dentures (**Dreyer et al 1978, Bredfeldt GW et al, 1992**)

⦿ **Pathogenesis** (**International Scholarly Research Network, 2011**)**:-**

- In **Intracellular Collagen Degradation Pathway,** Phenytoin induces a decrease in the Ca^{2+} cell influx leading to a reduction in the uptake of folic acid, thus limiting the production of active collagenase.

- The drug decreases collagen endocytosis through induction of a lower expression of **$\alpha_2\beta_1$-Integrin** by fibroblasts (**T. Kato et al, 2005**), which functions as a specific receptor for **Collagen Type I** in fibroblasts acts in the initial step of collagen phagocytosis & provides an adhesive interaction between fibroblasts & collagen (**M. Ogino et al, 2005**)
- In the **Extracellular Collagen Degradation Pathway**, other matrix metalloproteinases (MMPs) than collagenase are also responsible for the degradation of collagen fibers (**C. M. Kanno et al, 2008**)
- The enzymatic activities of MMPs are controlled by a tissue inhibitor (TIMP) whose function is to antagonize the actions of MMPs (**C. M. Kanno et al, 2008**)
- In **2005, Kato et al.** showed that the gene expression of MMP-1, 2 & 3 was reduced by phenytoin administration, while the TIMP-1 mRNA was markedly augmented.
- In accordance, macrophages pretreated with phenytoin & then exposed to LPS have lower production of MMPs than not treated controls (**R. Serra et al, 2010**)
- Phenytoin Induced Gingival Overgrowth are fibrotic (**P. C. Trackman & A. Kantarci, 2004**)
- Phenytoin also increases the production of IL-6 & IL-8 by fibroblasts [**T. Modeer et al, 2000**].
- IL-6 is capable of activating the proliferation of T & B lymphocytes, & it has been associated with fibrosis in various organs.
- IL-8 is chemotactic for polymorphonuclear neutrophils & T cells & it is associated with fibrosis in the liver & kidney [**G. Lonnemann et al, 1995**].
- The number of PMN & T cells is increased in gingival tissues induced by phenytoin [**R. E. Dill et al, 1988**], which contributes to the increased recruitment & activation of these cells by up-regulation of IL-6 and IL-8
- Myofibroblasts are highly differentiated cells that secrete large quantities of collagen (**T. A. Wynn, 2008**)
- Phenytoin exacerbates the normal tissue turnover/wound healing signals responsible for the appearance of myofibroblasts in gingiva (**R. E. Dill & A. M. Iacopino, 1997**) & hence results in overgrowth

Immunosuppressants

- Cyclosporine is a potent immunosuppressive agent
- Its effectiveness is due to a specific and reversible inhibition of T lymphocytes
- Specifically, Cyclosporin A inhibits Interleukin-2 (IL-2) synthesis & release at oral dosages of 10-20 mg/kg body weight per day (Serum concentrations of 100-400 ng/ml).
- At these therapeutic levels, Cyclosporin A also inhibits the ability of Cytotoxic T lymphocytes to respond to IL-2 while it has a sparing effect on T suppressor cells.
- In addition, Cyclosporin A produces immunosuppression by inhibiting the activation of macrophages & preventing the production of IL-1 receptors on the surface of T-helper cells (**De Camargo PM, 1989**)
- Cyclosporin A is widely used for prevention of organ transplant rejection, either as the primary immunosuppressant or in combination with steroid therapy (**Starzl TE et al , 1980**), graft-versus-host disease in bone marrow transplants (**Powles RL et al, 1980**) & disorders of the immune system, including insulin-dependent diabetes, Behcet's disease, rheumatoid and psoriatic arthritis, bullous pemphigoid and pemphigus, Crohn's disease, ulcerative colitis and pulmonary sarcoidosis (**Muller W, 1979, Nussenblatt RB et al, 1985, Rebuck AS et al, 1984, Stiller CR et al, 1983**)
- The adverse side effects of Cyclosporin A include **Gingival Overgrowth,** Hypertension, Nephrotoxicity & sometimes Hepatotoxicity
- The first cases of **Gingival Overgrowth** caused by Cyclosporin A reported by **Rateitschak-Pluss et al.** (**Rateitschak-Pluss et al., 1983**)
- These enlarged tissues are generally more hyperemic than the gingival tissues associated with phenytoin-induced overgrowth, occurs in approximately 30% of patients receiving the drug, is more frequent in children (**Schulz A et al, 1990**)
- Its magnitude is related more to the plasma concentration than to the patient's periodontal status (**Seymour RA et al, 1987**), ie if the plasma concentration exceeds **400 ng/ml** (**Seymour R &Heasrnan P., 1988**) or dose greater than **500mg/day** (**Daley TD, 1986**)
- Synergistic effects have been reported when **Cyclosporin A** is administered concurrently with **Calcium Channel Blockers** of the **Dihydropyridine derivatives** such as **Nifedipine**(**Slavin J & Taylor J, 1987**)

- Since fewer than 50% of patients taking Cyclosporin A develop gingival enlargement, the terms responders & non-responders have been used to identify these individual differences
- Patients who expressed **HLA-DR1** have a protective role against gingival overgrowth from Cyclosporin A, whereas those expressing **HLA-DR2** showed an increased risk for overgrowth (**Pernu HE et al, 1994**) which was later confirmed by **Cebeci I** in **1996**

⦿ **Pathogenesis**:-

- Cyclosporin A & its major metabolite Hydroxy-cyclosporine stimulates fibroblast proliferation (**Mariotti et al, 1998**)

- Cyclosporin A causes a significant increase in collagen synthesis with a specific rise in the level of **Type I Procollagen**(**Schincaglia GP et al, 1992**)

- Increased tissue levels of non-sulfated glycosaminoglycans occurs with Cyclosporin A exposure, contributing to the occurrence of increased connective tissue matrix (**Zebrowski EJ et al, 1984**)

- Increased gingival levels of **Platelet-derived Growth Factor-B** may be responsible for promoting fibroblast proliferation & production of extracellular matrix constituents in gingival overgrowth

- **Macrophage** plays a primary role in drug-induced gingival overgrowth through changes in phenotype & subsequent up-regulation of specific growth factors such as platelet-derived growth factor-B.

- **Plemons et al & Nares et al.** proposed that macrophage platelet-derived growth factor-B gene expression rather than an increase in the number of macrophages produce excess **Platelet-derived Growth Factor- B**

- Plaque induced gingival inflammation exacerbates the expression of drug-induced gingival overgrowth

- Dental plaque act as a reservoir for Cyclosporin A (**McGaw T et al, 1987**)

- Cyclosporin A inhibits the effects of Lipopolysaccharide upon fibroblasts.

- In concentrations where Lipopolysaccharide from dental plaque would normally be cytotoxic for fibroblasts, Cyclosporin A negates this effect & allows fibroblastic proliferation (**Bartold PM, 1989**)

⦿ **Histological Characteristics:-**

- The histological features of all drug-induced gingival overgrowth are comparable, consisting primarily of connective tissue with an overlying irregular, multilayered, parakeratinized epithelium varying in thickness.
- Epithelial ridges penetrate deep into the connective tissue, creating irregularly arranged collagen fiber bundles.

- The connective tissue is highly vascularized & focal accumulations of infiltrating inflammatory cells are seen (**Rateitschak-Pluss EM et al, 1983**)

- The predominant cell type in the inflammatory infiltrate is the plasma cell, with lymphocytes seen to a lesser degree.

- The mononuclear cell infiltrate demonstrates the presence of T lymphocytes and monocytes adjacent to the **Junctional Epithelium**, with virtually no B lymphocytes (**Friskopp J &Klintmalm G., 1986**)

- Cyclosporin A-induced gingival overgrowth is a consequence of hypersensitivity to the drug

- There is marked plasma cell infiltrate in the gingival tissues.

- The dimensional increase in gingival overgrowth is due to an increased production of amorphous ground substance by the fibroblasts, containing increased numbers of both sulfated & non-sulfated glucosaminoglycans, resulting from an increased release of histamine by mast cells (**William W. Hallmon& Jeffrey A. Rossmann, 1999**)

Calcium Channel Blockers

- It is a group of drugs specifically developed for management of cardiovascular conditions, including Hypertension, Angina Pectoris, Coronary Artery Spasm & Cardiac Arrhythmia (**Medical Letter, Amlodipine - New Calcium Channel Blocker, 1992**)

- Calcium channel blockers may be classified on the basis of their Chemical Composition (**Seymour RA, 1991 & Rees TD., 1993**):-

  Benzothiazepine derivatives (Diltiazem)
  Phenylalkylamine derivatives (Verapamil)
  Substituted Dihydropyridines(Amlopidine, Felodipine, Isradipine, Nicardipine, Nifedipine, Nitrendipine, Oxodipine, Nimodipine, Nisoldipine)

- Calcium channel blockers act by inhibiting calcium ion influx across the cell membrane of cardiac & smooth muscle cells, thereby interfering or blocking mobilization of calcium intracellularly (**Springhouse PA, 1997**)

- This results in dilatation of coronary arteries and arterioles, as well as decreased myocardial contractility & oxygen demand

- The primary undesirable side effect of the calcium channel blockers results from excessive vasodilatation, which manifests as facial flushing, dizziness, headache & edema (**Lewis JG., 1983**)

- First report that associated a Calcium Channel Blocker (Nifedipine) with the occurrence of gingival overgrowth was published in **1984** (**Ramon Y et al, 1984**)

- Five other agents in this class, including Amlodipine (**Seymour RA et al, 1994)**, Felodipine (**Lombardi T et al, 1991**), Diltiazem (**Rowman JM, 1988 &Bullon P, 1995**), Nitrendipine [**Brown RS, 1990** (Reported First Case)] & Verapamil (**Mehta A, 1992**) later showed similar side effects

- Human studies have not supported a relationship between dose or plasma levels of these agents and gingival overgrowth (**Rarclay S, 1992, Ellis JS et al, 1992, Dullon P et al, 1994**)

⦿ **Clinical Manifestations**

- The clinical features of the gingival changes reported in association with calcium channel blockers are similar among all agents of this class (**Van der Wall EE et al, 1985, Tagawa T et al, 1989**)

- The interdental papillae are initially affected, becoming enlarged and resulting in a lobulated or nodular morphology (**Seymour RA, 1991**).

- These effects are limited to the **Attached & Marginal Gingiva**, and are more frequently observed **Anteriorly**, especially on the **Facial** surfaces (**Lainson PA, 1986**)

- The enlarged gingival tissues are often accompanied by inflammatory changes associated with poor plaque control.

- As the tissues become progressively larger, plaque control becomes more difficult.

- The enlarged gingiva may extend coronally and partially or completely obscure the teeth, presenting aesthetic & functional difficulties for affected patient (**Lainson PA, 1986**)

- Overgrowth does not affect edentulous areas (**Wilson TG, Kornman KS, 1996**), but Nifedipine-induced gingival enlargement may be seen around dental implants (**Silverstein LH et al, 1995**)

- Increased severity of gingival overgrowth is seen when Nifedipine is combined with Cyclosporine A compared with Cyclosporin A alone (**Thomason JM et al, 1995**)

- The influence of dosage, age, duration of medication, length of time taken & amount of the calcium channel blockers in gingival crevicular fluid is unknown at present (**Ellis JS et al, 1992 & 1993**)

Pathogenesis

- Calcium Channel Blockers & Phenytoin have a common mechanism of action related to the ability of each of these agents to affect calcium metabolism (**William W. Hallmon& Jeffrey A. Rossmann, 1999**)

- Nifedipine, Phenytoin &Cyclosporin A reduce cytosolic calcium levels in gingival fibroblasts & T cells, thus interfering with T cell proliferation or activation & collagen synthesis by gingival fibroblasts (**Rarclay S et al, 1992**)

- Gingival overgrowth results from overproduction of extracellular ground substance characterized by increased presence of sulphated-mucopolysaccharides (glycosaminoglycan), collagen & abundant active fibroblasts (**Jones S., 1986**)

⦿ **Histological Characteristics**

- The histological features of all drug-associated gingival overgrowth are comparable (**Lucas RM et al, 1985 &Lundergan W., 1989**)
- The epithelium exhibits parakeratosis, proliferation & elongation of the rete ridges, which extend some distance into the lamina propria (**Nery EB et al, 1985**)

- Increase in epithelial width (normally 0.3 to 0.5 mm), inflammatory changes accompanied by edema, & infiltrates of lymphocytes & plasma cells is seen (**Van der Wall EE et al, 1985**)

- The epithelial thickening induced by Nifedipine (**Barak S et al, 1987**) & Cyclosporine A (**Belazi M et al, 1993 &Wondimu B et al, 1995**) is related to thickening of the spinous layer

- Connective tissue changes are similar to other drugs that result in gingival enlargement

Management Of Gingival Enlargement

- The treatment options for drug-induced gingival enlargement is based on the medication being used and the clinical presentation of each particular case.

- **Treatment Of Drug Induced Gingival Enlargement**

  - **Drug Substitution/Withdrawal**

- ✓ Firstly, consideration should be given to the possibility of discontinuing the drug (**Harel-Raviv M et al, 1995**) or of changing medication after consulting with the patient's physician

- ✓ Simple discontinuation of the offending agent is usually not a practical option but replacing it with another medication is better

- ✓ It may take from **1 to 8 Weeks** for resolution of Drug Induced Gingival Enlargement Lesions. (**Khocht A & Schneider LC, 1997**)

- ✓ Not all patients respond to this mode of treatment, especially those with long-standing gingival lesions. (**Katz J et al, 1997)**

- ✓ Alternative medications to **Phenytoin** include **Carbamazepine** (**Dahllof G et al, 1993**) &**Valproic Acid**, both of which have a lesser impact in inducing gingival enlargement

- ✓ If a change in Anticonvulsant Therapy is done, this should be accomplished gradually over a period of **2–3 months**.

- ✓ During this time there should be monitoring of **Serum Levels** of the **Anti Epileptics** & the occurrence of seizures (**Robin A. Seymour, 2006**)

- ✓ For patients on **Nifedipine,** other calcium-channel blockers such as **Diltiazem**&**Verapamil** may be viable alternatives since the prevalence of gingival enlargement associated with these drugs is less (**Nery EB et al, 1995**)

- ✓ Also, consideration may be given to the use of another class of antihypertensive medications than**Calcium-channel Blockers**, none of which are known to induce gingival enlargement (**Paulo. M. Camargo et al, 2001**)

- ✓ **Angiotensin Converting Enzyme Inhibitors** is a viable alternative to **Nifedipine** for renal transplant patients (**William W. Hallmon& Jeffrey A. Rossmann, 1999**)

- ✓ Drug substitution options for Cyclosporin are more limited (**William W. Hallmon& Jeffrey A. Rossmann, 1999**)

- ✓ **Cyclosporin**- Induced Gingival Enlargement can spontaneously resolve if the drug is substituted by **Tacrolimus** (**Hernandez G et al, 2000 & 2003**)

- ✓ If any drug substitution is attempted, it is important to allow for **6–12 months** to elapse between discontinuation of the offending drug & the possible resolution of gingival enlargement (**Hernandez G et al, 2000**) before a decision to implement surgical treatment is made

o Elimination Of Local Factors

- ✓ The presence of drug-induced gingival enlargement is associated with pseudo- pocket formation, the possibility of periodontitis to develop due to plaque accumulation exists & hence emphasis should be laid on **Plaque Control**

- ✓ Good oral hygiene and frequent professional removal of plaque decreases the **Degree Of Gingival Enlargement** present & improves overall gingival health (**Seymour RA & Jacobs DJ., 1992, Dongari A et al, 1993**)

- ✓ A **3 Month** interval for **Periodontal Maintenance Therapy** is recommended for patients taking drugs associated with gingival enlargement (**Hall EE., 1997**)

- ✓ Each recall appointment should include detailed oral hygiene instructions and complete periodontal prophylaxis, with supra & subgingival calculus removal as needed.

- ✓ In case of pediatric patients, parents should also receive oral hygiene instructions.

o Medications Used In Non Surgical Management Of Cyclosporine A & Phenytoin Induced Enlargement

✓ Cyclosporine A Induced Enlargement

- For **Cyclosporine A** induced gingival overgrowth, 7- day course of **Systemic Metronidazole** were tried in **Four** cases of **Renal Transplant** patients with success (**Wong W et al, 1994**)but periodontal condition was not taken into account

- Hence it is difficult to describe the nature of enlargement, ie drug-induced or secondary to underlying gingival inflammation

- **Azithromycin** is another antibiotic that has been evaluated in the management of **Cyclosporine A** induced gingival overgrowth

- A clinical study (**Mesa FL et al, 2003**) concluded that a **7 day** course of Azithromycin does not affect the remission of drug-induced gingival overgrowth but does act on concomitant bacterial infection & hence reduces inflammation

- Since drug induced gingival overgrowth is a recurrent & continuous problem, repeated doses of antibiotics in the management of this unwanted effect, especially in immunosuppressed patients is not justified (**Robin A. Seymour, 2006**)

✓ Phenytoin Induced Enlargement

- Chlorhexidine mouthwash (0.2% w / v) is of benefit in preventing **Phenytoin** induced gingival overgrowth, especially after surgery (**O'Neil TC & Figures KH, 1982**)

- Phenytoin inhibits **Folic Acid** metabolism, but the mechanism is uncertain

- Folic acid (**1 mg / ml mouthwash**) is more efficacious than systemic administration for preventing gingival enlargement (**Robin A. Seymour, 2006**)

- Folate may reduce gingival inflammation by binding to the plaque-derived endotoxins. (**Robin A. Seymour, 2006**)

- This action may, in turn, reduce gingival overgrowth

- Patients with a **Low Baseline Plasma & Red Blood Cell Folate**show a better gingival response to **Topical Folic Acid** than patients with normal levels (**Drew HJ et al, 1987**)

Surgical Treatment (**Paulo M. Camargo et al, 2001**)

- ✓ For gingival enlargement persisting, despite drug substitution attempts & good plaque control need to be treated by periodontal surgery, ie either:-

  i) Gingivectomy

  ii) Periodontal Flap

- ✓ Any of the two surgical techniques must be chosen on a case-by-case basis & should take into consideration the extent of area of surgery, the presence of periodontitis, the presence of osseous defects combined with the gingival enlargement lesions & the position of the bases of the pockets in relation to the existing mucogingival junction.
- ✓ In general, **Small Areas, Up To Six Teeth Presenting** with drug-induced gingival enlargement where there is **No Evidence Of Attachment Loss & therefore No Anticipated Need To Perform Osseous Surgery** can be effectively treated with the **Gingivectomy Technique**

- ✓ An important aspect in selecting gingivectomy as the surgical technique to treat drug-induced gingival enlargement cases is the **amount of keratinized tissue** present.

- ✓ Itis recommended that **at least 3 mm** of keratinized tissuein the **apico-coronal direction remain** after the surgical procedure is concluded.

- ✓ Therefore, if the **initial gingivectomy incision n**eeds to be placed in **close proximity** to or **at the Mucogingival Junction, this technique is** contraindicated

➢ The Gingivectomy Technique Used In The Treatment Of Drug-induced Gingival Enlargement

- ❖ Following administration of local anesthesia, the deepest point in each pocket (radicular and interproximal surfaces) is marked on the external gingival wall using a pocket marker or a probe.

- ❖ The series of bleeding points obtained with pocket marking works as a guideline for the initial scalloped external bevel incision. This incision is accomplished with the Kirkland knife or a 15 blade (if angulation permits).

- ❖ A sulcular incision follows the initial external bevel incision & the release of the interproximal tissue can be achieved with an Orban knife.

- ❖ Following excision of most of the enlarged tissue with curettes, gingivoplasty is performed to restore the physiological contour of gingiva

- ❖ Gingivoplasty is performed with surgical scissors, tissue nipper & high-speed diamonds

- ❖ Following this procedure, meticulous scaling & root planing is done

- ❖ Finally, periodontal dressing is placed at surgical area

- Gingivectomy or gingivoplasty can also be performed by **Electrosurgery** or by a **Laser** device
- **Larger Areas Of Gingival Enlargement, ie, More Than Six Teeth Or areas** where **Attachment Loss Combined** with **Osseous Defects,** in **Areas With Limited Keratinized Tissue** & any situation in which the **Gingivectomy Technique** may result in the **Elimination Of All Keratinized Tissue** &consequent creation of **Mucogingival Problems** should be treated with the **Periodontal Flap**.

- **Periodontal flap** is a also indicated in the treatment of drug-induced gingival enlargement so as to **Assist Tooth Eruption In Younger Patients.**

- Due to the increased thickness of the gingival tissues, it can be difficult for **Normal Eruption Forces** to push a tooth though the mucosa.

- The result of that process may be the **Soft Tissue Impaction** of the tooth **Apical** to or at its **Normal Occluding Position**

- If the **Gingivectomy** technique is done in this situation, it would result in the complete elimination of all keratinized tissue & the creation of a mucogingival problem.

- The **Flap Technique** allows for the complete exposure of the impacted tooth or teeth by apically positioning the thinned out flap without compromising the mucogingival status of the area

➢ Periodontal Flap Technique For The Treatment Of Drug Induced Gingival Enlargement

- Following administration of local anesthesia, sounding of the underlying alveolar bone is performed with a periodontal probe to determine the presence and extent of osseous defects.

- ❖ The initial scalloped internal bevel incision is made with a No. 15 blade at least 3 mm coronal to the mucogingival junction

- ❖ The same blade is then used to thin the gingival tissues in the buccolingual direction

- ❖ This thinning process should be carried out to the mucogingival junction.

- ❖ At the mucogingival junction level, the blade establishes contact with the alveolar bone and a full- or split-thickness flap is elevated.

- ❖ The gingival tissue collar, which is attached to the bone & teeth, is removed with the curettes.

- ❖ Following scaling, root planing & osseous recontouring when necessary, flaps are positioned right on top of the alveolar crest and sutures are placed using an interrupted or continuous technique with absorbable or non-absorbable materials

- ❖ Despite being technically more demanding, healing following the periodontal flap is comfortable for the patient & there is less chance of postoperative hemorrhage.

- ❖ It is also possible for the patient to resume mechanical oral hygiene earlier with the periodontal flap due to primary closure of the surgical wound.

- ⦿ **Maintenance**

- o Recurrence of drug-induced gingival enlargement is common in surgically treated cases (**Rees TD & Levine RA., 1995**) though in general, surgical results are maintained for **at least 12 months**

- Meticulous home care (**Nishikawa S et al, 1991**), Chlorhexidine Gluconate rinses (**Saravia ME et al, 1990**) & professional cleaning can decrease the rate and the degree at which recurrence occurs.

Conclusion

- Certain Group of medications have the potential to contribute to the development of gingival overgrowth

- Adverse aesthetics and impaired function are associated with the presence of drug-induced gingival enlargement.

- Comprehensive treatment of these cases is multidisciplinary in nature

- First the nonsurgical approach is considered, including the removal of local factors and discontinuation of the offending drug.

- If the nonsurgical approach is not effective, periodontal surgery in form of the gingivectomy or periodontal flap procedures can effectively reduce the enlarged gingival tissues.

- The maintenance of treated cases includes meticulous home care and professional recalls.

- Surgical re-treatment of recurrence areas is sometimes considered

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