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DRUG-INDUCED GINGIVAL OVERGROWTH-A REVIEW

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Abstract: Gingival overgrowth is characterized by the accumulation of extracellular matrix in gingival connective tissues, particularly collagenous components with various degrees of inflammation.
Gingival overgrowth can result due to inflammation, infections, neoplasms, endocrinal, drug induced.
Drug-induced gingival overgrowth is a side effect of drugs used in treatment of systemic diseases.
The common drugs which cause a gingival overgrowth are,
- Anticonvulsants (phenytoin),
- Immunosuppressive agents (cyclosporine A),
- Calcium channel blockers in CVS diseases.

Keywords:Neoplasms,Anticonvulsants,Immunosuppressive agents,Calcium channel blockers.

1. INTRODUCTION

- Increase in size of the gingiva is a common feature of gingival disease. The many types of gingival enlargement can be classified according to etiologic factors and pathologic changes as follows:
- I. Inflammatory enlargement
- A. Chronic.
- B. Acute.
- II. Drug –induced enlargement
- III.Enlargements associated with systemic disease or conditions.
- A . Conditioned enlargement.
- Pregnancy
- Puberty
- Vitamin C deficiency
- Plasma cell gingivitis
- Nonspecific conditioned enlargement (pyogenic granuloma)
- B. Systemic disease causing gingival enlargement.

- 1.Leukemia.
- 2.Granulomatous diseases.
  (e.g.,Wegener's granulomatosis,sarcoidosis).
- IV. Neoplastic enlargement (gingival tumors).
- Bening tumors.
- Malignant tumors.
- V. False enlargement.

The gingiva and associated soft tissues of the periodontium may be enlarged in response to various interactions between the host and the environment. Of the pre-disposing factorsassociated with disproportionate, disfiguring and functionally compromising overgrowth of gingival tissues selected

- (a) anticonvulsant drugs,
- (b) potent immuno suppressant (cyclosporin A) have generated the most investigative attention in the scientific community.
- (c) calcium channel blockers.

DRUGS CAUSING GINGIVAL OVERGROWTH

I. Anticonvulsants

- Hydantoins : Ethotoin
  Mephenytoin
  Phenytoin
- Succinimides : Ethosuccimide
  Methosuccimide
  Phensuccimide.
- Valproic acid
- II. Immuno suppressants
- Cyclosporin A
- III. Calcium channel blockers.
- Dihydropyridine derivatives
- Amlodipine Nimodipine
- Felodipine Nisoldepine
- Nicardipine Nitrendepine
- Nifidepine
- Benzothiazine derivative – Deltiazem
- Phenylalkylamine derivative – Verapamil Hcl
- Puolijoki H, Siitonen L,[(1)]Studied withdrawal and substitution of the drug along with improved oral hygiene has been successful in many cases of nifedipine gingival overgrowth.
- Westbrook P, Bednarczyk E, Carlson M, et al,[(2)]Studied regression ofnifedipine-induced gingival hyperplasia following switch to a same class calcium channel blocker, isradipine.

2. DISCUSSION

Anticonvulsants

- Phenytoin (5-diphenyl phenytoin) is an anticonvulsive drug widely used in the control of epilepsy and other convulsive disorders**.** [3]
- It is also used in the management of trigeminal, glossopharyngeal and post herpetic neuralgia and occasionally to treat ventricular arrhythmias.
- Gingival overgrowth is the main side effect following the usage of phenytoin. Other unwanted effects of phenytoin include cardiac arrhythmias, depression of the CNS, drowsiness, hirsuitism and osteomalacia.

ORAL CHANGES

- The earliest signs of gingival change are, (a)soreness and tenderness start occurring 2-3 weeks after phenytoin therapy.
- (b) During the first 6-9 months, there is initial enlargement of the interdental papillae facially and lingually which is less frequently accompanied by increased thickening of the marginal tissue.
- (c) Affected papillae may become enlarged to the point that they contact, resulting in the clinical presence of pseudoclefts.
- (d) Overgrowth usually diminishes as it approaches the mucogingival junction, but coronal progression may partially or totally obscure the crowns of the teeth**.**[4](Angelopoulos et al, 1972).
- (e) Affected tissues typically present a granular or lobulated surface.
- (f) The facial gingiva of the anterior sextants is more commonly affected and often results in esthetic disfigurement**.**[5](Butler et al, 1987)
- (g) The colour of the gingiva range from coral pink to a deep bluish red depending upon the amount of inflammatory infiltrate present**.**[6] (Esterberg and white, 1945)
- Enlargement of the gingival tissues may result in malpositioning of teeth and interference with normal masticatory function, speech and oral hygiene**.**[7]**(**Philstrom BL et al 1990)
- Relationship between patient's oral hygiene status and the incidence and magnitude of phenytoin induced gingival overgrowth is contradictory. Mouth breathing and other local factors such as crowding significantly relate to the occurrence of the overgrowth.

PATHOGENESIS

- The pathogenesis of cyclosporin induced gingival overgrowth is multifactorial and remains uncertain despite numerous investigations.
- Through selective immunosuppression, cyclosporin A has the ability to inhibit the production of interleukins , which are potent stimulators of collagenase.
- Cyclosporin A also affects androgen metabolism. It stimulates biosynthesis of DHT(dehydrothyrsiferol) from testosterone in gingival fibroblast. It leads to production of large amounts of collagen as well as production of inactive form of collagenase resulting in gingival overgrowth.
- Growth factors have been observed as a target for cyclosporin induced gingival overgrowth and their activation may play an important role in pathogenesis.

HISTOLOGICAL CHANGES

Composed primarily of connective tissue with overlying irregular multilayered, parakeratinized epithelium varying in thickness. Other histological factors includeacanthosis, with pseudo epitheliomatous proliferation, focal areas of myxomatous changes in sub epithelial tissue.

- Epithelial ridges penetrate deep into connective tissue, creating an irregularly arranged collagen fiber bundles.
- Connective tissue is highly vascularized and focal accumulation of inflammatory cells is seen. Predominant cell type is the plasma cell lymphocytes seen to a lesser degree.[8](Rateitschak-Pluss et al 1983).
- T-lymphocytes are seen adjacent to junctional epithelium.
- Accumulation of non- collagenous material and thickening of epithelium gingival overgrowth.

ORAL MANIFESTATIONS

The first case of cyclosporin induced gingival over growth were reported in the dental literature in 1983,[8](Rateitschak – Pluss et al). It commences as a papillary swelling that is more pronounced on the labial aspects of the gingiva than on the palatal or lingual aspect.[9] (Tyldesley and Rotter1984) .

- The swelling enlarges and adjacent papillae appear to coalesce giving the gingiva a lobulated appearance. Overgrowth is restricted to the width of the attached gingiva, but can extend coronally and interfere with the occlusion, mastication and speech and even cause migration of teeth.
- The incidence of cyclosporin induced gingival overgrowth varies between 25-50% depending upon drug dosage, plasma concentration, duration of therapy, method of assessing gingival enlargement, underlying periodontal status, age of the patient, medical status and genetic predisposition to be responders or non responders.

PREVENTION AND TREATMENT

Considerable evidence supports the fact that plaque induced gingival inflammation exacerbates the expression of drug induced gingival overgrowth. Inflammatory changes in the gingiva caused by plaque enhance the interaction between cyclosporin A and fibroblasts.**(10)**(McGaw et al1987, Bartold 1989, Seymour 1996)

- Prevention of Cyclosporin induced gingival overgrowth has focused on reduction in gingival inflammation.
- Significant improvement occurred in gingival enlargement following initial debridement and that strict plaque control prevented recurrence.**(11)**(Rateitschak Pluss et al 1983).
- Substituting cyclosporin A with Tacrolimus, gingival enlargement regresses spontaneously.**(12)**(Hernandez et al 2000).
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CALCIUM CHANNEL BLOCKERS

- These are group of drugs specifically used in the management of cardiovascular conditions like hypertension, angina pectoris, coronary artery spasm and cardiac arrhythmias, etc.

CLASSIFICATION

- Benzothia zepine derivatives (Diltiazem)

- Phenyl alkylamine derivatives (Verapamil)
- Substituted dihydropyridines (amlodipine, felodipine, isradipine, nicardipine, nifedipine, nitrendipine, oxodipine, nimodipine & nisoldipine).

MECHANISM OF ACTION

- Calcium channel blockers act by inhibiting calcium ion influx across the cell membrane of cardiac and smooth muscle cells thereby blocking the intracellular mobilization of Ca^{++}.
- It causes dilatation of coronary arteries & arterioles as well as decreased myocardial contractility and oxygen demand. The first report of occurence of gingival overgrowth associated with calcium channel blocker (nifedipine**).**[13]was reported by(Ramon et al. 1984.)
- Gingival overgrowth has been reported in 15-83% (composite average 42.5%) of patients taking Nifedipine (Barak et al.1987; Fattore et al.1991), approximately 21% of patients taking diltiazem (Steel et al. 1994) and about 4% of those medicated with verapamil.

ORAL MANIFESTATIONS

- Gingival enlargement appears shortly immediately after the start of therapy and decreases on withdrawal of drug **.**[14]**(** Lederman et al 1984.)
- Interdental papilla become enlarged giving a lobulated or nodular morphology.
- Limited to attached and marginal gingiva occurs frequently in anterior facial surfaces.
- Enlarged gingiva extend coronally and obsures the teeth either partially or completely.
- Overgrowth does not appears to affect the edentulous areas.
- Nifidepine induced gingival enlargements has been reported around dental implants**.**[15](Silverstain et al 1995 ***)***

HISTOLOGICAL FEATURES

- Gingival overgrowth results from over production of extracellular ground substances characterised by increased presence of sulphated mucopolysaccharides (Glycosaminoglycans) and collagen and abundant active fibroblasts**.**[16](Lucas et al 1985 and Jones et al 1986)
- Histological features of all drug associated gingival overgrowth are comparable. Although the connective tissue changes may be predominant, the epithelium exhibits parakeratosis, proliferation and elongation of the rete ridges, which extend some distance into the lamina propria.
- There was a thickening of spinous cell layer, slight to moderate hyperkeratosis,fibroblastic proliferation and fibrosis of lamina propria **.**[17](Barak et al 1987).
- Electron microscope showed increase in ground substance**.**[18](Lucas et al 1985)

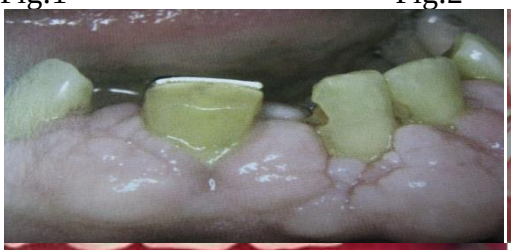
PREVENTION AND TREATMENT

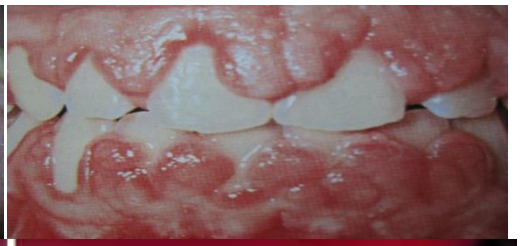
- Control of inflammation and maintenance of effective oral hygiene are key factors in preventing and managing gingival overgrowth.
- Surgical reduction of the overgrowth tissues is frequently necessary and consist of conventional gingivectomy and / or laser gingivectomy.
- Regression of nifedipine induced gingival overgrowth has been reported following a change in medication to isradipine, a companion dihydropyrdine calcium channel blocker.

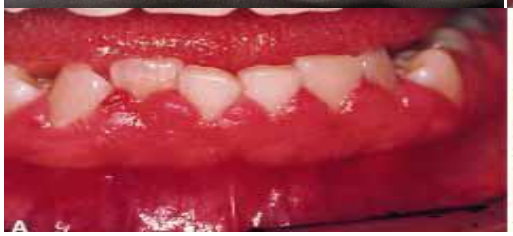
3. CONCLUSION

- Three very different groups of pharmaceutical agents have been associated with the occurrence of gingival overgrowth in susceptible individuals. These agents areanticonvulsants, cyclosporin A and calcium channel blockers. Despite their pharmacological diversity, all three types of drugs have a similar mechanism of action at cellular level, where they inhibit intracellular calcium ion influx causing a common side effect upon a secondary target tissue, such as gingival connective tissue. Treatment and prevention begins with removal of plaque and calculus, establishing good oral hygiene practices and frequent recalls for supportive therapy. Although non surgical treatment may be favorable, often surgical removal of over grown tissues to accomplish an esthetic and functional results may be required.
- Anterior sextants is commonly affected,Fig:1,2,3,4.

Fig:1 Fig:2







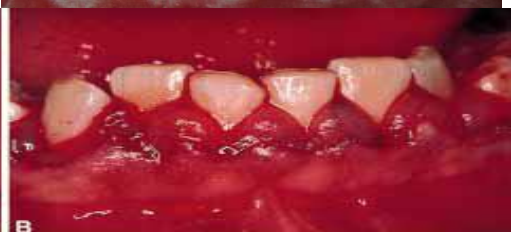


Fig:3 Fig:4

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