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Review Article

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Drug induced gingival enlargement

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ABSTRACT

Gingival enlargement can occur by taking certain medications, leading to problems in speech, eating, teething functions and aesthetics. Anticonvulsants, calcium channel blockers and immunosuppressants are the most reported medications resulting in gingival enlargement. Appearance of gingival enlargement is clinically and histologically similar in these three drugs. Although their primary tissue is not similar, a review of the literature reveals their identical pharmacological mechanisms at cellular level and similar behavior in the secondary target tissue like gingiva. They are different in risk factors such as bacterial plaque, doses, patient age and gender, prescription and host genetics. This study evaluates the clinical appearance and histology, drug mechanisms, side effects, risk factors and treatment by these three drugs separately and in combination.

Keywords: Drug, Gingival enlargement

INTRODUCTION

Gingival enlargement or overgrowth is a common symptom of gingival diseases. Based on etiologic factors and pathological changes, different types of gingival enlargement include inflammatory, drug-induced and neo-plastic enlargements as well as the enlargements associated with diseases or systemic conditions such as gingivitis plasma cells and pyogenic granuloma (1).
More than 20 types of drugs associated with gingival enlargement have been reported, including anticonvulsants, immunosuppressants and calcium channel blockers (2).

The major clinical and microscopic characteristics of gingival enlargement caused by various drugs are similar (1).Usually, enlargement starts from interdental papillae; in absence of inflammation, it is berry-like, rigid, pale pink, springy with fine lobulated surface which does not tend to bleed. However, unavailable oral health often causes secondary inflammation in the enlarged gingiva; in this case, the gingiva will tend to bleed.

Histopathologically, gingival epithelium involves acanthosisnigricans and enlarged ratpag; dense collagenous masses and increased number of fibroblasts as well as new blood vessels and amorphous matrix can be seen connective tissue.

There is disagreement on the role of plaque. Some studies suggest that plaque is essential in development of gingival enlargement; the unreported plaque in edentulous areas supports this (2, 3). However, Gearge Sam et al observed low inflammatory symptoms and good oral hygiene associated with gingival enlargement, which questions the prerequisite for the presence of bacterial plaque (3).

1.Anticonvulsants

Anticonvulsants include phenytoin, valproic acid, phenobarbitone**,** vigabatrin and carbamazepine. The incidence of gingival enlargement was reported in phenytoin (50%), phenobarbitone (5%) and the rest rarely (4).

Due to the high incidence of phenytoin-associated gingival enlargement, a majority of studies has been conducted on this drug. Phenytoin is prescribed for treatment of epilepsy other than petitmal, non-epileptic seizure control in head trauma, Reye's syndrome, neurotic pains and dysrhythmias resistant to lidocaine and procainamide (5).Phenytoin is the drug of choice for its effectiveness, low price and availability (6).Phenytoin-associated gingival enlargement was first reported in 1939 by Kimball (7).

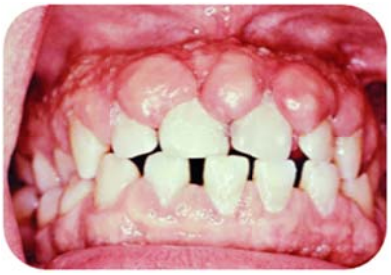

Figure 1: Phenytoin-associated gingival enlargement

1.1. Clinical Changes

Clinical changes of phenytoin-induced gingival enlargement appear within 2-3 months of drug use and maximizes after 12-18 months (11).

1.2. Histopathological Changes

Histologically, there is proliferation of fibroblasts; however, fibroblast to collagen ratio is similar to normal tissue (2).

1.3. Risk Factors

Studies on phenytoin-induced gingival enlargement have addressed risk factors such as multidrug anticonvulsants, accumulation of bacterial plaque, host genetics and dropped levels of serum folic acid (1).

1.3.1. Dosage

Some studies have found that pre-threshold serum phenytoin was directly associated with gingival enlargement, while no association was found between post-threshold phenytoin and gingival enlargement (2). Girgis et al found a direct relationship between gingival enlargement and phenytoin dosage in 50% of patients, while no relationship and even an inverse relationship was found in the rest 50% (8).

1.3.2. Age

Phenytoin-induced gingival enlargement is more common in young people (9).

1.3.3. Multidrug Treatment

Phenytoin administration with other anticonvulsants was not significant on severity of gingival enlargement (10).

1.3.4. Plaque
Studies show that the activity and responsiveness of fibroblasts to phenytoin is eliminated under non-inflammatory conditions. However, good plaque control does not reduce and prevent gingival enlargement (2).Efforts to find a particular species of bacteria associated with phenytoin-induced gingival enlargement have been failed. Cases without gingival enlargement was observed even in people with poor plaque control and treated with phenytoin (11).

1.3.5. Genetics
Specific subgroups of fibroblasts have been proposed in connective tissue as a predisposing factor responding to phenytoin (12).

1.4. Pharmaceutical Mechanism and Pathogenesis
Laboratory studies on phenytoin-induced gingival enlargement have observed fibroblast-like cell proliferation, proliferation of epithelium, increased synthesis of glycosoaminoglycans sulfate and reduced degradation of collagen following production of non-active fibroblastic collagenase (2).

Other studies observed the increased synthesis of protein fibroblasts, particularly collagen, through direct stimulation of mast cells (4). Pharmacological mechanism of phenytoin suppresses the central nervous system without affecting the sensory nerves. At the cellular level, phenytoin suppresses Na-K-ATPase pump and inhibits the excitability of motor nerve cells and pump-related materials into the cell (13, 14).

Molecular-cellular studies showed the increased expression of TGFB in lamina propria. Increased PDGF-BB as a mitogenic factor and chemotaxis of gingival fibroblasts as well as the increasedIL1B and IL6 resulting in the increased synthesis of collagen and glycosoaminoglycans were reported (1).

Phenytoin-induced reduction of folic acid leads to degenerative changes in the epithelium exacerbated in the presence of inflammatory factors. The increased synthesis of testosterone metabolite by fibroblasts can cause gingival enlargement in people who take phenytoin (11).

1.5. Side Effects
In addition to gingival enlargement, phenytoin can accelerate megaloblastic anemia. In non-convulsive people, phenytoin can accelerate gingival wound healing and increase the tensile strength of abdominal wounds (2).

1.6. Treatment
Studies found that gingival enlargement disappeared spontaneously 4 months after stopping the drug (8). Treatment protocol starts with periodontal therapy Phase I; then, the neurologistre places phenytoin by another drug. The patient is monitored for one month to check the convulsions; then, the periodontal therapy Phase II including gingivectomyor periodontal flap and full debridement starts (6).

The recommended time for follow-up is once in every 3 months (15); another study has recommended monthly follow-up in the first six months and then once in every 3 months (16).

Although chlorhexidine compounds are effective in preventing gingival enlargement, the toothpastes containing chlorhexidine have not been successful; in fact, once the gingival enlargement develops, no chemicals will be effective in its elimination.

Topical antihistamines, corticosteroids and topical stannous fluoride had little success.

Folic acid increases metabolism and secretion of phenytoin; however, studies did not show a significant effect on reduction, while systemic folic acid will reduce the therapeutic effect of phenytoin. Topical folic acid has been known effective in improving phenytoin-induced gingival enlargement (11),because topical folic acid provides fibroblasts with higher concentration of folate, compared to oral folic acid (17, 18).

2. Immunosuppressants
The immunosuppressant cyclosporine has been known as a cause of gingival enlargement with 25-30% prevalence in adults and over 70% in children (4).

Cyclosporine is administered to prevent transplant rejection and treat autoimmune diseases. Due to the administration of cyclosporine for a wide range of diseases, it is called wonder drug (2, 7).

Cyclosporine-induced gingival enlargement was first reported in 1983 by Rateitschak (19).

2.1. Clinical Appearance

Pebbly or papillary cyclosporine-induced gingival enlargement is associated with the presence of hyphal candida invading the gingival epithelium. The gingiva of people taking cyclosporine is more hyperemic and more prone to bleeding on probing than that of people taking phenytoin (4).

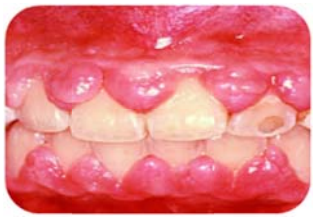

Figure 2: Cyclosporine-induced gingival enlargement

2.2.Histopathology

Cyclosporine-induced gingival enlargement is often seen in connective tissue and secularization as well as focal inflammatory cells particularly plasma cells (7). Pisantly argued that gingival enlargement is simply due to the epithelial acanthosis and accumulation of extracellular matrix and the connective tissue does not change in size (31).

2.3. Risk Factors

The studies on cyclosporine addressed the risk factors such as dose, bacterial plaque, age, multidrug treatment, gender and graft.

2.3.1. Dosage

There is disagreement on the relationship between severity of gingival enlargement and the dose in blood and saliva. Some studies have reported that development of gingival enlargement requires a threshold of drug concentration in blood plasma, while its severity is not associated with the dose (20).The dosage 500 mg is considered as the threshold (2). However, some researchers found no relationship between cyclosporine dose and development of gingival enlargement (21).

2.3.2. Plaque

Although bacterial plaque is not considered as an etiologic factor in cyclosporine-induced gingival enlargement, it can be a predisposing factor (22); however, it is insignificantly associated with the severity of gingival enlargement (20).

2.3.3. Age

Mild gingival enlargement has been reported at least in one area of the mouth in patients younger than 20 years who took cyclosporine and less in patients over 40 years due to the growth hormone and high metabolism of fibroblast in childhood and adolescence (22, 7).

2.3.4. Multidrug Treatment

Taylor reported that cyclosporine administered with nifedipine caused a 6-fold increase in development of gingival enlargement (24, 23); moreover, prednisolone and azathioprine, which are commonly administered with cyclosporine, considerably influence gingival enlargement (25).

2.3.5. Gender

Unlike Rotter who reported 38% prevalence of cyclosporine-induced gingival enlargement in women and 17% in men, other studies considered gender neutral (22).

2.3.6. Graft

Studies consider the graft received effective on the prevalence of gingival enlargement. Gingival enlargement is less common in bone graft than the transplanted kidney, heart and lungs. Its prevalence has been reported 97% in the transplanted heart and lung (27, 26).

Molecular-cellular studies on the recipient tissue showed that gingival enlargement was more severe in positive HLA 37 than positive HLA DR1 (28, 29).Mismatched HLA in the donor tissue and recipient tissue had no effect on the severity of gingival enlargement (30).

2.4. Pharmaceutical Mechanism (Pathogenesis)

The mechanism of cyclosporine is not fully understood; however, blood and cellular immunity response seems to be influenced by selective and reversible inhibition of T helper cells (2).Igs independent of T cells and T supressors have not been affected in studies in vivo (7).

Secretions of the enlarged gingiva contain more IL6 compared to normal gingiva. IL6 increases the proliferation of fibroblasts and synthesis of glycosoaminoglycans. Recent human studies have shown reduced levels of MMP1 and MMP3 in secretions of the enlarged gingiva and increased level of TGFB resulting in accumulation of extracellular compounds (1, 4).

2.5. Treatment

The severity of cyclosporine-induced gingival enlargement progresses to 12 months after starting the drug and remains unchanged thereafter. By stopping the treatment, gingival enlargement recovers and even disappears (22).A study reports that the metronidazole administered for 7 days reduces gingival enlargement (32).In another study, the azithromycin administered for 5 days improved the enlargement (33).

3. Calcium Channel Blockers

Calcium channel blockers include nifedipine, felodipin, verapamil, diltiazem, amlodipine and isradipine. Development of gingival enlargement has been reported in nifedipine (6-15%), diltiazem (5-20%), verapamil (less than 5%), felodipin and amlodipine (rarely) and isradipine (not so far) (4).

Calcium channel blockers are administered for treatment of cardiovascular diseases such as hypertension, angina pectoralis, coronary artery spasm and arrhythmia by reduced burden on the heart, decreased systemic vascular resistance, smooth muscle vasodilatation and reduced heart rate (2, 4, 34).

Nifedipine-induced gingival enlargement was first reported by Lederman in 1984 (22).

Studies onnifedipine-induced gingival enlargement addressed the risk factors such as bacterial plaque, doses, age, gender and genetics.

3.1. Clinical Changes

Clinical changes appear 1-3 months after administration. Edentulous areas have not been seen (34); however, it can affect the mucus around the implant (42).

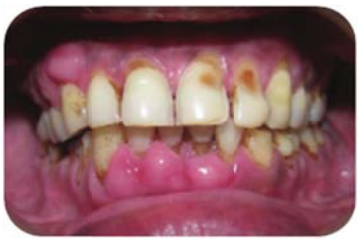

Figure 3:nifedipine-induced gingival enlargement

3.2. Histopathological Changes
In the study conducted by Barak, the gingival epithelium proliferation was more responsible for gingival enlargement than connective tissue proliferation (43).An increase was reported in production of acid mucopoly saccharides and the number of cytoplasmic secretory granules (44).

3.3. Risk Factors
3.3.1. Bacterial Plaque
Shaftic reported gingival enlargement after taking nifedipine despite good plaque control (35), while Thomas reported a positive association between Nifedipin-induced gingival enlargement and oral hygiene and degree of gingival inflammation (7).

3.3.2. Dosage
Gingival enlargement occurs by taking30-100 mg nifedipin per day (22). There is disagreement on the increased gingival enlargement and nifedipin dose; some reported it as dependent on the dose (26,3,7) and some reported low correlation (37), while Bencini found no relationship between dose and increased gingival enlargement (38).

3.3.3. Age
Age is not known as a risk factor; note that nifedipinis usually prescribed for middle aged and older people (39).

3.3.4. Gender
Gingival enlargement is reported in men more than women(49). Lshida found that the threshold serum dose for gingival enlargement was lower in men than women (41).

3.3.5. Genetics
In some people, there are certain subgroups of fibroblasts, which are more sensitive to nifedipine and increased collagen production (3); this can be associated with HLA. Moreover, the enzyme polymorphism, cytochrome P450, is an effective genetic factor (34).

3.4. Therapeutic Mechanisms and Pathogenesis
Calcium channel blockers affect the Ca metabolism by reducing the intracellular Caflow and limiting the production of active collagenase (35). The inflammatory cytokines IL6 and IL1b play an important role in physiological response to calcium channel blockers (4); this highlights the role of bacterial plaque in calling cytokines and gingival enlargement (34).

The lipophilic nifedipine easily penetrates into the cells, compared to the polarized amlodipine; this structural difference plays an important role in drug-induced gingival enlargement. A large portion of amlodipine remains in the tissue and it is not observed freely in the circulation. Amlodipine rarely reaches the threshold required to cause gingival enlargement (34).

3.5. Side Effects
Administration of nifedipine in patients with diabetes Type II increases the risk of periodontal destruction (2). In addition to gingival enlargement, tachycardia and facial redness can be seen in patients taking these drugs (34).

3.6. Treatment
Bernal reported full recovery of gingival enlargement 4 months after stopping the drug (45).No relationship was found between dosage and duration of treatment (22).

Treatment protocol includes replacement by isradipine if no abnormality develops in blood pressure control; otherwise, surgical intervention is recommended (34).

In 40% of cases, recurrence will occur 3-6 months after surgical treatment (46).Recurrence risk seems to be higher in people with poorer oral hygiene (34).

4. Contraceptives
Gingival enlargement associated with contraceptives was first reported in 1967 by Lynn (47).Despite case reports, contraceptives are not known as inducers of gingival enlargement. After a few months of administration, the

cumulative dose will be 6-15 times greater than the expected and the effects will disappear by stopping the administration (22).

5. Erythromycin

One study reported the erythromycin-induced gingival enlargement (48). However, given the widespread use of erythromycin, this can not introduce erythromycin as an inducer of gingival enlargement.

CONCLUSION

Mechanism of intracellular Ca and Na ion flow has been considered as a common pathogenesis in three drugs inducing gingival enlargement (3). Now, heterogeneity of fibroblasts is known as a key factor in the etiology of drug-induced gingival enlargement (2).Regardless of its cause, gingival enlargement can cause problems in controlling plaque, chewing, teething, speech and aesthetics (1).Treatment is based on the administered drug and clinical characteristics and it can include non-surgical treatments, surgical treatments as drug replacement (49).Non-surgical treatments include oral hygiene instruction, scaling and smoothing the root surface, systemic antibiotics such as azithromycin and metronidazole, as well aschlorhexidine2 times a day (49).

To replace the drug, an urologist should be consulted. Carbamazepine and valproic acid can be a good alternative for phenytoin. In case of unsuccessful non-surgical treatments, lack of alternatives, in the dental soft tissue impaction or aesthetic considerations, periodontal treatment Phase II including gingivectomy/gingivoplasty or periodontal flap is considered (49).The surgical technique adopted is based on the extent of gingival enlargement, bone defects and the distance between pseudopocket and mucogingival base.

Indications of gingivectomy include involvement of less than six teeth, lack of bone defects and far pseudopocket and mucogingival bases. Gingivectomy can be replaced by surgery, laser diode, carbon dioxide or argon. Indications of periodontal flap include involvement of more than 6 teeth, bone lesions and when gingivectomy ends in removing a large amount of keratinized tissue (49).

The recommended post-operative follow-up is monthly in the first six months and then once in every 3 months. In 40% of nifedipine- and cyclosporine-induced gingival enlargements, recurrence occurred after 18 months. Risk factors of recurrence include early age, gingivitis and lack of regular visits. The chlorhexidine0.12%twice a day can help prevent post-surgical recurrence (4).

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