

Review of cyclosporine induced gingival overgrowth

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ABSTRACT

The cyclosporine-A is the most effective immunosuppressant drug of choice. Due to its property of selective immunosuppressibility, it prevents graft rejection and yet leaves the recipient with enough immune activity to combat bacterial infection. It is efficacious in other autoimmune disorders like Type I diabetes mellitus, psoriasis, multiple sclerosis, rheumatoid arthritis etc. Experts have estimated that as many as one billion person's world wide over wide age group may be taking CsA on a chronic regimen within next decade. The use of CsA is associated with adverse side effect which includes gingival overgrowth. Hence here an attempt is made to review available literature about Cyclosporine and its side effects and to highlight the issue of cyclosporine induced gingival overgrowth, the incidence of which is expected to rise, and which the periodontists will have to deal with in near future.

Introduction

The use of cyclosporine-A is associated with adverse side effects that include hyperplasia and fibrosis of pericardial, renal connective tissue as well as oral gingival tissues. The most prevalent side effect which is going to worry a periodontist is its induction of gingival overgrowth. This side effect was first reported in dental literature by Rateischak Plus et al (1983) after the causal observation made by Calne and Stazl et al in 1981.[1] Since then this issue is widely studied and researched but the exact cause and underlying mechanism are still uncertain. There are lot of controversies regarding its cause, pathogenesis, variables, risk factors, histopathology and management. . Here an attempt is made to review the different opinions and to bring about the known facts.

Cyclosporine and gingival overgrowth

Association of drug with gingival overgrowth

1. The association between cyclosporine therapy and gingival overgrowth was first noticed in early eighties when the drug was undergoing initial evaluation in transplant surgery(starz 1980, calne 1981)
2. The first few cases were reported in literature in 1983 by Rateitschak-Pluss et al. They studied 50 kidney transplant patients most of whom developed enlargement in 4-6 weeks of therapy.

Incidence

The prevalence of the overgrowth varies in different studies between 8% to 85% and is generally about 30%. It is said to be lower than phenytoin induced gingival overgrowth but higher than calcium channel blockers induced gingival overgrowth.[2] The higher prevalence of CsA maybe implicated to its usage in wide

variety of conditions and in all the age groups. Incidence varies from study to study with range between 28-81 %

Synergistic effects have been reported when CsA is administered concurrently with calcium channel blockers of dihydropyridine derivatives like nifedipine. Incidence is 48% with calcium channel blockers .Incidence is 100% in patients under the age of 15 and 50 % in patients over age of 5. Higher incidence in females(28%)than males (18%).[2] Such a finding suggests a possible interaction between cyclosporine, sex hormones and gingival fibroblasts. Alternatively fibroblasts from young patients may be more susceptible to the drug. Underlying medical problem is an important determinant of cyclosporine induced gingival overgrowth.

Clinical manifestations

It commences as a papillary enlargement which is more pronounced on the labial aspect of the gingival than the palatal or lingual surfaces. The papillary enlargement increases and adjacent papillae appear to coalesce. This gives the gingival tissues a lobulated appearance. Overgrowth is restricted to the width of attached gingiva but can extend coronally and interfere with the occlusion, mastication and speech. It is also noted that the overgrowth associated with canine teeth (with predilection on buccal surface) was significantly greater than that around central incisors(Fig.1).[3] The hyperplastic gingival tissue often shows marked inflammatory changes(Fig.2). They bleed readily on probing.

Overgrowth rarely happens in edentulous patients. It appears that periodontal ligament is essential for gingival overgrowth since CsA induced proliferation of oral tissue does not occur at sites distant from teeth.[4]

The gingival changes usually occurs within 3 months from the onset of treatment, however they can start as soon as 1 month and as early as 1 week. CsA induced gingival overgrowth is a progressive

enlargement over a period of months and typically approached plateau state at 1 year. Overgrowth should develop within 6 months and not beyond it. Underlying periodontal hyper responsiveness to CsA must necessarily emerge very soon or never. It has been said that CsA induced overgrowth is cyclic in nature. There is an inverse relationship between gingival overgrowth and months since the graft. It was argued that the reduction in gingival overgrowth could be the result of a positive effect of time in reducing the sensitivity of the periodontium to the hyper productive effect of CsA. The duration of CsA therapy increases the chance of overgrowth. In children 100% prevalence of overgrowth in subjects taking Cs for longer than 3 months.

Relationship of overgrowth to drug dosage and plasma concentration

Some baseline concentration of cyclosporine is required to stimulate the hyperplastic changes, but once overgrowth develops no correlation exists between increase in the dose and the severity of lesions. Overgrowth was more likely to develop if the plasma concentration of CsA exceeded 400ng/ml.[5]

Role of plaque in gingival overgrowth

The role of plaque in CsA induced overgrowth is uncertain. It has been speculated that the lipophilic CsA may be concentrated and retained as a reservoir in dental plaque. Thus plaque may play an important role in development of gingival overgrowth. Proper oral hygiene can minimize the severity but cannot prevent the occurrence of it in 'responders'. Studies have shown that plaque scores are more important than drug dose as determinant of gingival changes in cyclosporine treated patients. There might be an interaction between the drug and dental plaque, which may serve as a reservoir for cyclosporine that is later released by stimulated saliva flow.[6] The concentrations of cyclosporine in dental plaque were found to be higher than those in blood and other tissues. The stepwise regression model also identifies gingival inflammation as an important determinant of the severity of gingival overgrowth. Inflammatory changes in gingiva enhance interaction between the drug and fibroblasts. Proper oral hygiene minimizes severity but not prevent overgrowth. Also CsA inhibit negative effect of cytotoxicity by lipopolysaccharide on fibroblasts. Possibility that metabolite produced by bacterial species exposed to CsA may alter fibroblast metabolism.



Fig.1 Picture showing gingival hyperplasia.

Cyclosporine-A and periodontal status

It has also been proposed the administration of cyclosporine could enhance the progression of periodontitis, once patient immune system is suppressed. But other factors compensate for antibody deficiency-cells are possible targets of CsA, and they constitute 30% of cells in gingiva of patient with advanced periodontal disease. Therefore reduction in fibroblast toxicity, osteoclastic activation and bone resorption and reduction in inflammatory infiltrate in gingiva occur when CsA is administered.

Histopathology of CsA gingival overgrowth

Cyclosporine enlargement result from accumulation of non-collagenous extracellular material and thickening of epithelium. hence it's a overgrowth and not true hyperplasia. The overgrowth is a consequence of individual hypersensitivity to drug, hence abundant amorphous substance rather than fibrous material , with a marked plasma cell infiltrate in the gingival tissues is seen. There is increased release of histamine by mast cells. Histologically the enlargement has shown different picture according to the stage of its development. Initial tissue had more of extracellular matrix and glycosaminoglycans component and as the overgrowth progressed the cellularity increased. The fibroblasts density was seen in later stages. Most of the studies have supported the presence of high number of plasma cells indicating hypersensitive reaction to drug. Subset of nonfunctional T-cells is also seen. Hence the term "dimensional increase of gingival tissue" is more appropriate for this type of overgrowth.[7]

Drug induced alterations in gingival connective tissue homeostasis.

CsA causes increased procollagen gene expression and increases level of type I procollagen secretion from fibroblasts via cyclophilin receptors. CsA affects increase in synthesis of TIMP. Fibroblasts show characteristics of active protein synthesis and secretion. Selective immunosuppressive properties of CsA leads to inhibition of interleukins which in turn has the ability to stimulate collagenase from fibroblasts. Hence less collagenase secretion and more collagen production will lead to altered connective tissue homeostasis.[7]

Genetic predisposition CsA and OL-17 its metabolite react with phenotypically distinct subpopulation of gingival fibroblasts. HLA antigen expression in population determines the susceptibility of an individual to CsA overgrowth. Those with HLDA-DR2 showed increase risk.[7]

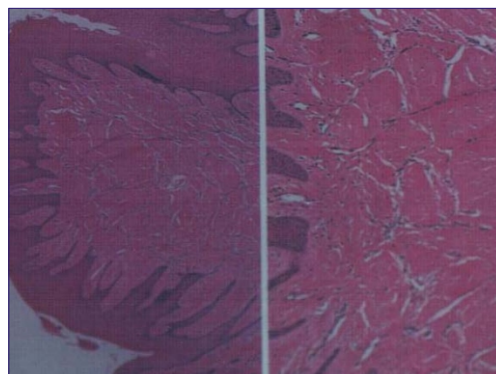


Fig.2 Histopathological picture showing inflammatory changes.

Role of Growth factors on drug action Macrophage regulated Platelet derived growth factors induces fibroblast proliferation and synthesis.

Disruption of fibroblast cellular $\text{Na}^+/\text{Ca}^{2+}$ flux

Disruption of fibroblast cellular $\text{Na}^+/\text{Ca}^{2+}$ flux increases collagenase production. Calcium and sodium exchange affects local foliate concentration in the tissue.[8]

Thus pathogenesis supports the hypothesis that is multifactorial. The three significant factors are important in the expression of these gingival changes, notably drug variables; plaque induced inflammatory changes in gingival tissues and genetic factor.

Prevention and treatment

Following is the protocol

A. Before CsA therapy

1. Educate the patient.
2. Instruct proper oral hygiene methods.
3. Oral prophylaxis remove all calculus deposits and stains.
4. Replace any defective restoration.
5. Modify existing orthodontic or prosthodontic appliance to reduce irritation.

6. Treat any mouth breathing habits present.

B. During cyclosporine therapy-closely monitor patients oral hygiene.

C. In patients where severe gingival hyperplasia develops despite preventive measures.

1. Gingivectomy performed to remove excess gingiva.
2. If cessation of CsA therapy is planned then observe regression of the gingival hyperplasia for minimum of 6 months after cessation before planning any definitive treatment. The nature of organ transplants often means that alternative therapy or dose reduction is not possible. Some patients can use more conventional immunosuppressive such as steroids and azothioprine but survival rates are not as good. New immunosuppressive such as FK 506 tacrolimus, rapamycin may offer some hope.[9,10] Reports indicates that short course of azithromycin improved gingival overgrowth. The association of lower dosages of cyclosporine and higher dosages of prednisolone and azothioprine in some patients might indicate potential to use multiple therapies as a means of controlling the regression of this condition

Comparison with other drugs

Three very different groups of drugs have been associated with gingival overgrowth. They have similar mechanism of action at calcium ion influx have similar clinical manifestation. Treatment also remains the same with following difference.[11]

Anticonvulsants Cyclosporine Calcium channel blockers. Acts on Na^+/K^+ ATPase pump and inhibit Ca^{2+} uptake by direct action on Ca^{2+} channel binds to calmodulin and decreases intracellular Ca^{2+} . does not directly act on Ca^{2+} channel. Direct action on calcium channel receptors Younger age group Wider age group Middle age group Dense resilient, stippled with granular surface. More hyperemic than phenytoin associate with inflammatory changes.

Increased proliferation of fibroblasts, increased collagen fibers (normal appearing tissue) Increase in collagen matrix and connective tissue elements, increased amorphous substance with fibrous material and plasma cell. Same as phenytoin but more collagen present

Conclusion

The problem of drug induced gingival overgrowth is an ever challenging condition due to the presence of underlying medical situation, they have to be managed with utmost care and expertise taking into consideration the general physical health of patient. Also from periodontal point of view, the presence of overgrowth if untreated can harm the underlying periodontal structures by allowing numbers of pathogenic bacteria to multiply beneath the overgrowth. Hence role of periodontist is to prevent the occurrence of overgrowth and treat the existing overgrowth to prevent future loss of teeth.

References

1. Rateitschak P, Hefti E M et al. Initial observation that cyclosporine-A induces gingival enlargement in man. *J Of Clin Periodontol*.1983;10:237-46.
2. Marshall R I, Bartold P M. Review on medication induced gingival overgrowth. *Oral Disease* 1998;4:103-51.
3. Seymour RA, Jacobs D J. Cyclosporin and the gingival tissues. *J Clin Periodontol* 1992;19:1-11.
4. Daley T D, Wysode G.P. Cyclosporin therapy.its significance to the periodontist. *J Periodontol* 1984;55:708-12.
5. AdamsD, Davis G. Gingival hyperplasia associated with Cyclosporin A. *Brz Dent J*. 1984:157-89.
6. Seymour R A, Smith D G. The effect of plaque control programme on the incidence and severity of Cyclosporin induced gingival changes. *J Clin Periodontol*.1991;18:107-10.
7. Hallman W W, Rossmann J A. The role of drugs in the pathogenesis of gingival overgrowth: A collective review of current concepts. *Periodontol* 2000 1999;21:176-96.
8. Brown R S, Beareo W T et al. On the mechanism of drug induced gingival hyperplasia. *J Oral Pathol Med*.1991;20:201-9.
9. Daley C G. Resolution of cyclosporin A induced gingival enlargement following reduction in CsA dosage: Case Report. *J Clin Periodontol* 1992;19:142-5.
10. MacGraw T, Lam S et al. Cyclosporin induced gingival overgrowth: correlation with dental plaque scores, gingivitis scores and cyclosporine levels in serum and saliva. *Oral Surg Oral Med Oral Pathol* 1987;64:293-7.
11. Hassell T M, Hefti A F. Drug induced gingival overgrowth: old problem, new problem. *Cri Rev Oral Bio and Med* 1991;2(1): 103-37.
12. Cebeci I, Kantarci A et al. Clinical effects of periodontal therapy on the severity of cyclosporine A-Induced Gingival Hyperplasia. *J Periodontol*.1999;70:587-93.

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