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REVIEW ARTICLE

CYCLOSPORIN INDUCED GINGIVAL OVERGROWTH: A REVIEW OF LITERATURE

Dr. Poonam M. Singh and *Dr. Ankita V. Deshmukh

D.Y. Patil University School of Dentistry, D.Y. Patil Vidyanagar, Sector- 7, Nerul (East), Navi Mumbai- 400706, Maharashtra, India

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ABSTRACT

Gingival overgrowth as a side effect of medication taken for non-dental reasons is a very commonly occurring condition. The drugs most commonly associated with this condition are anticonvulsants like phenytoin, immunosuppressants like cyclosporin and antihypertensive drugs such as calcium channel blockers. Cyclosporin is a selective immunosuppressant which is sued to prevent rejection following organ transplant procedure. Various hypotheses have been considered in the pathogenesis of gingival overgrowth induced by cyclosporin. These include presence of different subsets of fibroblasts, role of pro-inflammatory cytokines and matrixmetalloproteinases. Plaque accumulation is also thought to play an important role in the pathogenesis of gingival overgrowth. More recent investigations have hypothesized the role of mast cells, androgens, growth factors etc,. in the pathogenesis of cyclosporin induced gingival overgrowth. However, there is no clear understanding of the proposed hypotheses and further research is essential to establish a clear pathogenesis of gingival overgrowth and provide better and more precise design for its prevention and treatment. The following review presents the pharmacodynamics and pharmacokinetics of cyclosporin, its role in prevention of graft rejection and in the pathogenesis of gingival overgrowth with various modalities available for the treatment of the same.

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INTRODUCTION

Gingival diseases include a group of complex entities which are caused by various etiologic factors and display a characteristic set of signs and symptoms which may overlap in different conditions and may be complicated by plaque accumulation and presence of other local etiologic factors (Mariotti, 1999). Drug induced gingival overgrowth or enlargement occurs in whole or in part from systemic drug use (The American Academy of Periodontology, 2001). It has been observed that the drugs causing enlargement are mostly those prescribed for non-dental use (Marshall and Bartold, 1998; Bharti and Bansal, 2013). Although the exact pathogenesis of drug induced gingival enlargement is yet to be established, various factors such as age, oral hygiene, genetic constitution, presence of inflammation may influence the relationship between the causative drug and the gingival tissues[4]. The presence of a different subset of fibroblasts which respond differently to the drugs has been studied repeatedly by several investigators. It has also been observed that all individuals do not respond to the drug in a similar way.

Corresponding author: Dr. Ankita V. Deshmukh,
DY Patil University School of Dentistry, DY Patil Vidyanagar, Sector-7, Nerul (East), Navi Mumbai- 400706, Maharashtra, India.

There is always a difference in the severity and the extent of the condition among the group of individuals in which it occurs (Bharti and Bansal, 2013). The drugs that are known to cause gingival enlargement include anticonvulsants like phenytoin, sodium valproate, phenobarbitone, etc., immunosuppressant drugs such as cyclosporin and calcium channel blockers like nifedipine, felodipine, amlodipine, to name a few (Bharti and Bansal, 2013; Newman *et al*., 2006). The aim of the following review is to compile and present, from available literature, the hypothesized pathogenesis of gingival enlargement caused by cyclosporin with details on the clinical features, differential diagnosis and treatment of the enlarged gingival tissues.

Cyclosporin

Cyclosporin is a cyclic polypeptide with 11 aminoacids, obtained from a fungus and introduced by Borel in 1977 as a highly selective immunosuppressant which has markedly reduced the possibility of rejection of organ transplantation (Tripathi, 2008; Seymour *et al*., 1988). It has also been used as a second line of drug in the treatment of autoimmune diseases, like, severe rheumatoid arthritis, uveitis, bronchial asthma, inflammatory bowel disease, and in psoriasis, especially to suppress acute exacerbations (Tripathi, 2008; Suzuki *et al*.,

2009). Cyclosporin selectively suppresses cell mediated immunity, prevents graft rejection and leaves the recipient with enough immune activity to combat bacterial infection (Tripathi, 2008). The immunosuppressive effect of cyclosporin can be attributed to down regulation of the transcription factor NFAT through inhibition of calcineurin, repressing the production of interleukin – 6 (IL-6) in T- cells (Suzuki *et al*., 2009). Cyclosporin consumption has been known to have a number of side effects such as neurotoxicity, hepatotoxicity, nephrotoxicity, hypertension and gingival overgrowth[9]. Gingival overgrowth resulting from cyclosporin intake was first reported in 1983 by Seymour *et al* and occurring in 25-81% of patients (Ponnaiyan *et al*., 2015; Seymour and Jacobs, 1992). The prevalence rate of gingival overgrowth with cyclosporin has been found to be between 8% and 100%[9,] (Kataoka *et al*., 2005; Wright *et al*., 2005).

Role of Cyclosporin In Prevention of Graft Rejection

Cyclosporin is a selective immunosuppressant with a weak antimicrobial activity and it can be administered orally, intramuscularly or intravenously (Ponnaiyan and Jedadeesan, 2015). It has been mainly used following organ transplantation to prevent the rejection of the grafts. It has been proven from by several investigators that the selective activity of Cyclosporin is on the response of the T lymphocytes with little or no action on the B lymphocytes (Ponnaiyan and Jedadeesan, 2015; Britton *et al*., 1982). T cell mediated rejection of the graft takes place in the following steps (Seymour and Jacobs, 1992)

Recognition of antigen (graft tissue) as foreign material.

Processing of antigen by macrophages with the subsequent production and release from the cell of Interleukin-1 (IL-1)

IL-1 activation of precursor cytotoxic T-lymphocytes which acquire receptors for Interleukin -2 (IL-2)

Activation of T-helper lymphocytes with the production and release of IL-2, which is accentuated by IL-1.

The clonal amplification of activated cytotoxic T-lymphocytes which causes cell mediated lysis and graft rejection. The activation of suppressor T-lymphocytes which can modulate these responses. Cyclosporin inhibits many of the stages outlined above, acting both at cellular and molecular level. The drug inhibits interleukin 2 (IL-2) synthesis at concentrations between 10-20ng/ml. At higher concentrations, cyclosporin inhibits the ability of cytotoxic T-lymphocytes to respond to IL-2. However, the mechanism of this inhibition is uncertain.

Clinical Features

Cyclosporin induced gingival enlargement manifests usually in the first three months of the consumption of the drug (Bharti and Bansal, 2013; Dongari-Baqtzoglou *et al*., 2004; Seymour *et al*., 1992). The enlargement begins as a papillary swelling that is more prominent on the labial aspect of the gingiva than on the palatal or the lingual aspects. As the swelling enlarges, the adjacent papillae appear to join together and give the gingiva a lobulated appearance and also leads to the formation of pseudo-clefts. The enlargement is limited by the width of attached gingiva, but it may extend coronally and interfere with occlusion, mastication and speech. Cyclosporin induced gingival overgrowth has not been reported in edentulous subjects till date (Boltchi *et al*., 1999). When uncomplicated by inflammation, the lesion is mulberry shaped, firm, pale pink and resilient with a minutely lobulated surface and no tendency to bleed (Bharti and Bansal, 2013; Newman *et al*., 2006). The enlarged tissue make it difficult for the patient to maintain adequate oral hygiene thus resulting in secondary inflammatory process which further complicates the overgrowth caused by the drug. It not only adds to the bulk of the tissue but also produces red discolouration, increased tendency to bleed and obliteration of surface demarcations (Bharti and Bansal, 2013; Newman *et al*., 2006).

Histopathologic Features

Histopathologically, it is observed that the increase in gingival tissue volume is primarily due to a connective tissue response, rather than epithelial cell layer involvement (Bharti and Bansal, 2013). There is excessive accumulation of extracellular matrix proteins such as collagen or amorphous ground substance (Bharti and Bansal, 2013). This is mainly because of deficient degradation of collagen and other matrix components (Gnoatto *et al*., 2007). The overlying epithelium appears irregular, multilayered and of variable thickness. In some areas the epithelial ridges penetrate deeply into the sub-epithelial connective tissue. Focal accumulations of inflammatory cells is observed with plasma cells being the most predominant cell type (Boltchi *et al*., 1999).

Radiographic Features

If the gingival enlargement is uncomplicated by inflammatory reaction caused by local irritants, no specific radiographic findings are seen since it only affects the soft tissues. If an underlying periodontitis is present, loss of alveolar bone is radiographically evident (Pawlak *et al*., 1990).

Pathogenesis

Although cyclosporin induced gingival enlargement is one of the most commonly occurring adverse effect of a systemic medication, there is not clear cut understanding of the pathogenesis. However, various investigations and research work conducted over the years has supported the hypothesis that the gingival enlargement is multifactorial. Since the three major drugs causing overgrowth i.e., phenytoin, cyclosporin and calcium channel blockers have a similar mechanism of action which is their action on the calcium and sodium ion flux, it may prove to be the key in understanding why dissimilar drugs cause a common condition (Bharti and Bansal, 2013). Also, the severity and the extent of the condition depends on how well an individual maintains their oral hygiene. In the recent classification, it has been categorized as plaque induced gingival disease modified by medication (Bharti and Bansal, 2013; Dongari-Baqtzoglou, 2004; Armitage, 1999).

Role of fibroblasts (Bharti and Bansal, 2013)

It has been hypothesized that the susceptibility of the gingival tissues to overgrowth by Cyclosporin consumption may be due

to the presence of differential proportions of fibroblast subsets. These fibroblasts respond differently to the drug.

Role of inflammatory cytokine (Bharti and Bansal, 2013)

There is an increase in the proportion of pro-inflammatory cytokines in inflamed gingiva which are known to play an important role in the pathogenesis of gingival enlargement when simultaneously exposed to the drug. Interleukin 1β (IL-1β) and interleukin 6 (IL-6) may play a role in the fibrogenic responses of the gingiva to cyclosporin. IL-6 appears to enhance proliferation of fibroblasts and exerts a positive regulation on collagen and glycosaminoglycans synthesis.

Role of matrix metalloproteinase Bharti and Bansal, 2013)

It has been postulated that these agents may interfere with the synthesis and function of collagenases.

Role of basement membrane integrity (Bharti and Bansal, 2013; Kantarci *et al*., 2011)

Higher numbers of basement membrane discontinuities in enlarged tissues were demonstrated by Kantarci *et al*. (2011). This disruption is accompanied by a discontinuous collagen type IV expression pattern and decreased laminin-5.

Role of mast cells (Bharti and Bansal, 2013; Subramani *et al*., 2013; Subramani *et al*., 2013)

Mast cells possess diverse roles ranging from proinflammatory to immunomodulatory. They participate in many inflammatory oral diseases, especially those associated with fibrosis. Upon their activation, they promote the local rennin angiotensin system and stimulate endothelin and other profibrotic mediators. Cyclosporin cn modulate local expression of rennin angiotensin system components such as angiotensinogen, angiotensin II and its receptors in gingival tissues, and gingival fibroblast cells.

Role of growth factors (Hallmon and Rossmann, 2000; James *et al*., 1998)

Activation of growth factors play an important role in the pathogenesis of Cyclosporin induced gingival enlargement. Increased levels of Platelet derived growth factor (PDGF) may be responsible for promoting fibroblast proliferation and production of extracellular matrix constituents in gingival overgrowth.

Role of androgens (Boltchi and Rees, 1999)

Alterations in androgen metabolism may account for increased propensity of cyclosporin induced gingival enlargement in children and adolescents. An increase in the biologically active form of testosterone has been found in the overgrown tissues of patients with Cyclosporin induced gingival enlargement.

Role of apoptosis (Bulut and Ozdemir, 2007)

It is also postulated that the extent of keratinocyte apoptosis and the decreased level of caspase-3 may play an important role in the gingivae of kidney transplant recipients with cyclosporin induce gingival enlargement. It was suggested that the hyperplasia is not caused by enhanced keratinocyte proliferation but by an enhanced life span or an alteration in the ability of cells to undergo apoptosis in a balanced manner.

DIFFERENTIAL DIAGNOSIS (Bharti and Bansal, 2013; Newman *et al*., 2006)

Inflammatory gingival enlargement: Acute inflammatory gingival enlargement may present clinically as a localized swelling with acute pain. Chronic inflammatory enlargement appears as a red or bluish red, soft, friable with smooth and shiny surface along with an increased tendency to bleed. Inflammatory gingival enlargement is generally seen as a secondary complication to some other type of enlargement and usually reduces after removal of the local irritants.

Idiopathic gingival enlargement: it affects all three parts of gingiva, namely, attached, marginal and papillary. The facial and lingual aspects of both the arches are usually involved but the enlargement may be limited to either maxillary or mandibular arch or a part of the arch. The enlarged gingiva is pick, firm and has a leathery consistency with a minutely pebbled surface. The cause of this type of gingival enlargement is unknown and may show hereditary basis.

Conditioned gingival enlargement: it usually occurs as a result of exaggeration of any systemic condition and alteration of the usual gingival response to dental plaque. This type of enlargement can be caused by hormonal changes (pregnancy, puberty), dietary defiency (Vitamin C deficiency) etc.

Systemic conditions causing gingival enlargement include leukemia, sarcoidosis and other granulomatous diseases due to the infiltration of diseased cells into the gingiva.

Neoplastic enlargement: It may appear as a slowly growing spherical mass that tends to be firm and nodular or hard, art like protuberance from gingival surface.

False enlargement: These are not true enlargement and may result from an increase in size of the underlying osseous or dental tissues. In such cases, only an increase in the size of the gingiva can be seen without any other signs of abnormality.

Treatment

The treatment of cyclosporin induced gingival enlargement can be considered under 2 categories: non-surgical and surgical.

Non surgical treatment: Non surgical treatment aims at the reduction of the bulk of the enlarged gingival tissues by substitution of the causative drug and thorough scaling and root planing to eliminate the local irritating factors, thus reducing the imflammatory component of the enlargement. Reduction in the dose of cyclosporin has been shown to be beneficial (Marshall Roderick *et al*., 1999), however, the nature of the organ transplant often means that alternative therapy or dose reduction may not be available. Newer

immunosuppressant agent such as tacrolimus may offer some hope as to date it has not been associated with gingival enlargement (Marshall Roderick *et al*., 1999; Greenberg *et al*., 2008). There is also preliminary evidence that the antibiotic azithromycin may aid in decreasing the severity of cyclosporin induced gingival enlargement (Camargo, 2000). The role of dental plaque and other local irritants has yet to be established in the pathogenesis of gingival enlargement. However, these factors elicit an inflammatory response from the tissues. This adds to the bulk of the enlarged tissue. The reduction of the inflammation although very important in itself also determines the necessity of surgical intervention and allows for a less hemorrhagic field during surgery (Marshall Roderick and Mark Bartold, 1999).

Surgical treatment (Bharti and Bansal, 2013; Newman *et al*., 2006)

It is essential to allow a period of at least 6-12 months to lapse between the stoppage or substitution of drug and possible resolution of the gingival enlargement **(**Bharti and Bansal, 2013; Newman *et al*., 2006**)**. Should the gingival enlargement persist despite substitution of Cyclosporin and maintenance of adequate oral hygiene, surgical intervention is indicated. Surgical treatment includes gingivectomy and periodontal flap procedures. The selection of the right procedure changes from case to case and depends on the area of enlargement to be treated, presence of periodontitis and alveolar bone loss in conjunction with the enlargement. Gingivectomy is indicated in a smaller area where up to six teeth are involved and there is no evidence of attachment loss. At least 3mm of keratinized tissue in the apico-coronal direction should be left after the procedure. It is contraindicated when the incision needs to be placed close to the mucogingival junction. Larger areas of gingival enlargement (more than 6 teeth) or where there is attachment loss and osseous defects, a periodontal flap is the treatment of choice. In small children or mentally challenged individuals, where conventional gingivectomy with scalpel or periodontal flap procedure cannot be performed, laser or electrosurgery can be employed to treat the gingival enlargement ((Bharti and Bansal, 2013; Hall, 1997).

Maintenance

Even though gingival enlargement can be treated by gingivectomy and periodontal flap procedures, not one of these techniques guarantee to prevent the recurrence of the condition. To decrease the rate of recurrence of the condition, it is essential for an individual to maintain adequate oral hygiene through proper home care, use of mouthwash and regular professional cleaning. A positive pressure appliance may also be used for about 8 hours daily to reduce the tendency to recurrence of the gingival enlargement (Hallmon and Rossmann, 2000).

Conclusion

Cyclosporin induced gingival enlargement can be considered as one of the most commonly occurring, unesthetic and functionally interfering side effect caused by the systemic use of s drug used for non-dental purpose. Due to lack of clear understanding of the pathogenesis of the condition, a gold standard treatment regimen cannot be established to reduce the severity and prevent its recurrence. Therefore, it is necessary to explore and evaluate the risk factors which could affect both, the prevalence and severity of the gingival enlargement. Further research work needs to be carried out to establish a clear pathogenesis so as to formulate better treatment modalities.

REFERENCES

Armitage, G.C. 1999. Development of a classification system for periodontal diseases and conditions. *Ann periodontal, 4*:1.

Bharti, V., Bansal, C. 2013. Drug induced gingival overgrowth: The nemesis of gingiva unravelled. *J Indian Soc. Periodontol,* 17(2):182-187.

Boltchi, F.E., Rees, T.D. and Iacopino, A.M. 1999. Cyclosporin- A induced gingival overgrowth. A comprehensive review. Quintessence Int30:775-783.

Britton, S. and Palacios, R. 1982. Cyclosporin A – usefulness, risks and mechanisms of action. Immunol Rev., 65:5-22.

Bulut, S. and Ozdemir, H. 2007. Apoptosis and expression of caspase – 3 in cyclosporin- induced gingival overgrowth. *J Periodontol,* 78:2364-2368.

Camargo, P.M. 2001. Treatment of drug induced gingival enlargement : esthetic and functional considerations. Periodontol 2000;27:131-138.

Dongari-Baqtzoglou, A. 2004. Research, Science and therapy committee, American academy pf Periodontology. Drug-associated gingival enlargement. *J Periodontol,* 75:1424-31.

Gnoatto, N., Lotufo, R.F.M., Matsuda, M., Penna, V. and Marquezini, M.V. 2007. Expression of cell surface heparin sulphate proteoglycans in human gingival overgrowth. *J Periodontont Res.,* 42:553-558.

Greenberg, K.V., Armitage, G.C. and Shiboski, C.H. 2008. Gingival enlargement among renal transplant recipients in the era of new- generation immunosuppressants. *J Periodontol,* 79:453-460.

Hall, E.E. 1997. Prevention and treatment considerations in patients with drug induced gingival enlargement. Current opinion in periodontology, 4:59-63.

Hallmon, W.W. and Rossmann, J.A. 2000. The role of drugs in pathogenesis of drug induced gingival overgrowth. A collective review of current concepts. Periodontol 2000; 21:176-196.

James, J.A., Irwin, C.R. and Linden, G.J. 1998. Gingival fibroblast response to Cyclosporin A and transforming growth factor β1. *J Periodont Res*., 33: 40-48.

Kantarci, A., Nseir, Z., Kim, Y.S., Sume, S.S. and Trackman, P.C. 2011. Loss of basement membrane integrity in human gingival overgrowth. *J Dent Res.,* 90:887-93.

Kataoka, K., Kido, J., Shinohara, Y. and Nagata, T. 2005. Drug induced gingival overgrowth. A review. *Biol Pharm Bull.,* 28:1817-21.

Mariotti A. 1999. Dental plaque induced gingival diseases. *Ann Periodontol,* 4:7-17.

Marshall Roderick, I. and Mark Bartold, P. 1999. A clinical review of drug induced gingival overgrowths. *Australian Dental Journal*, 44(4): 219-232.

Marshall, R.I. and Bartold, P.M. 1998. Medication induced gingival overgrowth. *Oral Dis.,* 4:130-51.

Newman, M.G., Takei, H.H., Klokkevold, P.R. and Carranza, F.A. Carranza's Clinical Periodontology, 10th Edition. W. B. Saunders Company 2006.

Pawlak, E.A. and Hoag, P.M. Essentials of Periodontics 4th Edition. The CV Mosby Company 1990; 62-68.

Ponnaiyan, D. and Jedadeesan, V. 2015. Cyclosporine A: Novel concepts in its role in drug- induced gingival overgrowth. *Dent Res J.,* 12:499-506.

Seymour, R.A. and Heasman, P.A. 1988. Drugs and the periodontium. *J. Clin. Periodontol,* 15(1):1-16.

Seymour, R.A. and Jacobs, D.J. 1992. Cyclosporin and the gingival tissues. *J Clin Periodontol,* 19:1-11.

Seymour, R.A., Heasman, P.A., MacGregor, I.M. 1992. Drugs, disease and periodontium. 1st Edition. Oxford University press.

Subramani, T., Rathanavelu, V., Yeap, S.K. and Alitheen, N.B. 2013. Influence of mast cells in drug-induced gingival overgrowth. Mediators Inflamm, 2013:275172.

Subramani, T., Senthilkumar, K., Periasamy, S. and Rao, S. 2013. Expression of angiotensin II and its receptors in cyclosporine- induced gingival overgrowth. *J Periodontol Res.,* 48:386-91.

Suzuki, A.M.M., Yoshimura, A., Ozaki, Y., Kaneko, T. and Hara, Y. 2009. Cyaclosporin A and Phenytoin modulate inflammatory response. *J Dent Res.,* 88(12):1131-1136.

The American Academy of Periodontology – Glossary of Periodontal terms, 4th Edition, 2001.

Tripathi, K.D. 2008. Essentials of Medical Pharmacology. 6th ed. New Delhi: Jaypee Brothers Medical Publishers (P) Ltd.

Wright, G., Welburg, R.R. and Hosey, M.T. 2005. Cyclosporin- induced gingival overgrowth in children. *International Journal of Pediatric Dentistry*, 15:403-411.

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