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Management of Cyclosporin -A Induced Gingival Overgrowth -A Case Report With Immunohistochemical Observations

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ABSTRACT

Cyclosporin A (CsA) is a potent immunosuppressant acting mainly on T lymphocytes by blocking intracellular processes of T cell activation. Gingival overgrowth (GO) is a well-documented side effect associated with the systemic use of cyclosporin A, an immunosuppressive drug extensively used for the prevention of organ transplant rejection, as well as in the treatment of immuno-related disorders. It would appear from both human and animal models that plaque-induced inflammatory changes have a significant part in the pathogenesis of such a disease. Gingival overgrowth is a clinical condition that poses functional and aesthetic problems. This article describes a case of cyclosporin A induced gingival overgrowth and its management.

Keywords: cyclosporin A, gingival overgrowth, immunohistochemistry, gingivectomy

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INTRODUCTION

Gingival overgrowth (GO) is defined as an increase in the size of the gingiva. Drug-induced gingival overgrowth (DIGO) is known as an adverse effect with three main classes of drugs: anticonvulsants such as phenytoin, antihypertensive calcium channel blockers such as dihydropyridines (nifedipine), diltiazem, and verapamil and the immunosuppressant cyclosporin. Such overgrowth is characterized by an accumulation of extracellular matrix (ECM) within the gingival connective tissue, especially the collagenous component, with various degrees of chronic inflammation. Cyclosporin A (CsA) is a potent immunosuppressant acting mainly on T-lymphocytes by blocking the transmission of certain cytoplasmic signals and interleukin-2 synthesis. It has been demonstrated that cyclosporin A blocks the immune system, acts on cytoskeleton and stimulates the production of ECM and transforming growth factor-β_1 (TGF-β_1). This cytokine, such as transforming growth factor-α (TGF-α), induces deposition of glycosaminoglycans (GAG), proteoglycans and collagen fibres in the ECM [1]. CsA is used for the prophylaxis of graft rejection in organ and tissue transplantation. The adverse effects of the drug include gingival overgrowth, nephrotoxicity, hypertension and hypertrichosis. The incidence of gingival overgrowth among transplant patients treated with CsA ranges from 6% to 81% [2].

Many plausible mechanisms for the cyclosporin A induced gingival overgrowth have been suggested. The drug may influence directly the inflammatory response [3]. The local inflammatory changes secondary to bacterial plaque may orchestrate the drug–fibroblast interaction [4, 5]. An additive action between the drug and the microbial plaque may be suggested [6]. CsA may stimulate both cell proliferation in the presence of bacterial lipopolysaccharide and the release of cytokines in inflamed gingival sites [7, 8].

There is limited immunohistochemical data available in the literature to evaluate the extent to which the drug and the plaque-induced inflammation separately contributes to the induction of GO [9]. In this article, we report a patient who developed gingival overgrowth after treatment with CsA for renal transplantation. The gingival histological features and immunohistochemical studies for vimentin and Ki-67 are also described.

Case Report:

A 42 year old male patient underwent renal transplantation (right kidney) 6 years back and was treated with cyclosporin A (Neoral 75 mg twice a day) and prednisolone (Wysolone 7.5 mg once a day). The patient now complains of gingival enlargement and bleeding for the past 2 years. Clinical examination revealed presence of local factors (plaque and calculus) on the teeth surfaces, pale pink gingiva with rolled out margins and bulbous interdental papilla (figure 1).

There was generalised bleeding on probing and gingival enlargement in the lower anterior region (Bokenkamp 1994- grade III in lower anterior region Seymour et al 1985- Hyperplastic Index of 24 %) [10, 11].

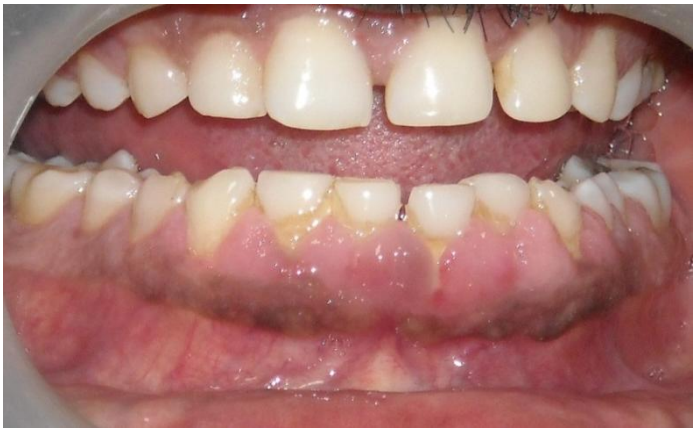

Figure 1: Intra oral view showing the presence of gingival enlargement

Histopathology:

Under local anesthesia an excisional biopsy of the overgrown gingiva was done. Upon excision, tissue samples were immediately embedded in 10% formalin before histologic and immunohistochemical examination. Light microscopy studies on the sections of overgrown gingiva were carried out by hematoxylin and eosin staining to determine the epithelial hyperplasia, the acanthosis and the degree of inflammation. The histopathology was suggestive of inflammatory fibroepithelial hyperplasia**.** The section showed dense fibrous connective tissue stroma along with foci of chronic inflammatory cell infiltrate consisting predominantly of plasma cells, moderate vascularity and areas of hemorrhage. The overlying parakeratinized stratified squamous epithelium was of variable thickness along with areas of pseudoepitheliomatous hyperplasia. (figure 2).

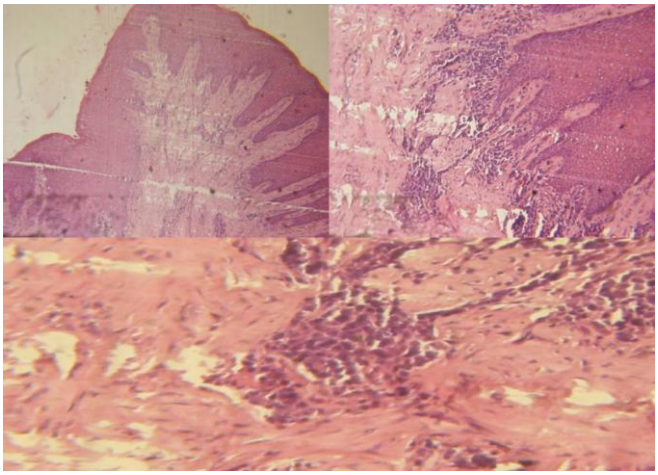

Figure 2: Histopathology of gingival tissue

Immunohistochemistry:

The excised gingival samples were embedded in paraffin blocks and tissue sections were obtained using a microtome. Immunohistochemistry examination was carried out using the antigen retrieval system. Vimentin (V 9 clone) and Ki-67 (Mib-1 clone) were used as primary antibodies. Vimentin is a member of the intermediate filament family of proteins. Vimentin is the major cytoskeletal component of mesenchymal cells. The Ki-67 protein (also known as MKI67) is a cellular marker for proliferation. It is strictly associated with cell proliferation. Immunohistochemically the gingival connective tissue stained moderately positive for vimentin and negative for Ki-67 (figure 3 and 4). These findings suggested that this disease may be the result of an increase in collagen synthesis by the fibroblasts

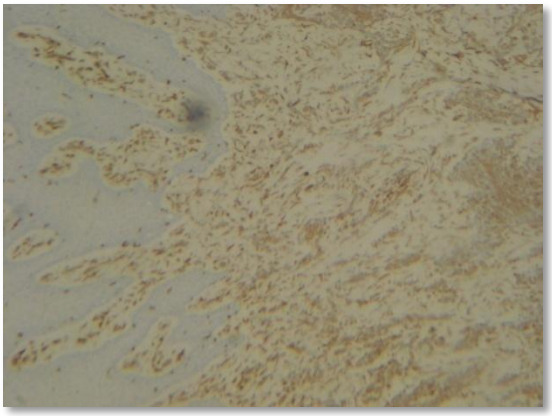

Figure 3 : Vimentin positive staining of gingival connective tissue

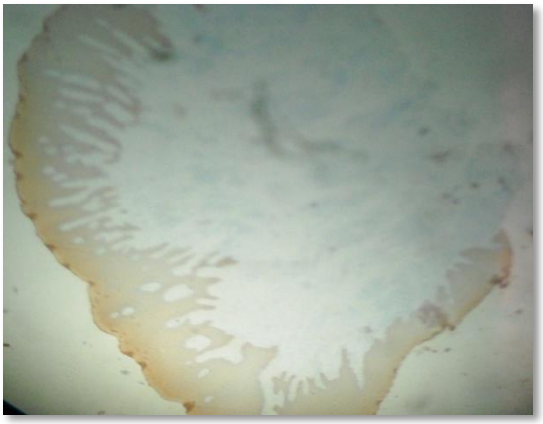

Figure 4: Ki-67 negative staining

Management:

The patient's physician was consulted and haematologic investigations were carried out, after which the patient was deemed medically fit to undergo periodontal surgical treatment. Under local anaesthesia full mouth scaling and root planing was done (figure 5). The patient was reviewed after a month and persistence of the gingival enlargement was seen in the lower anterior teeth region. Localised scalpel gingivectomy was done in the lower anterior teeth region and periodontal pack was given. The patient was reviewed after a week and wound healing was satisfactory (figure 6). The patient was reviewed at regular intervals and after 6 months there was no recurrence of gingival overgrowth in spite of the patient continuing to take CsA (figure 7). At this point a tissue sample of the gingiva was subjected to immunohistochemical examination. The immunohistochemistry examination was mildly positive for vimentin and negative for Ki-67 indicating that the proliferation of the cells in the connective tissue had decreased.

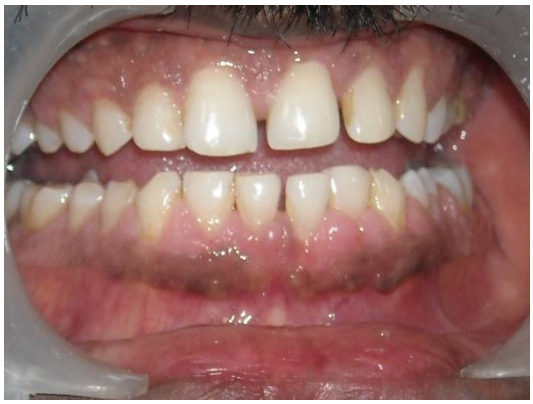

Figure 5: After scaling and root planing

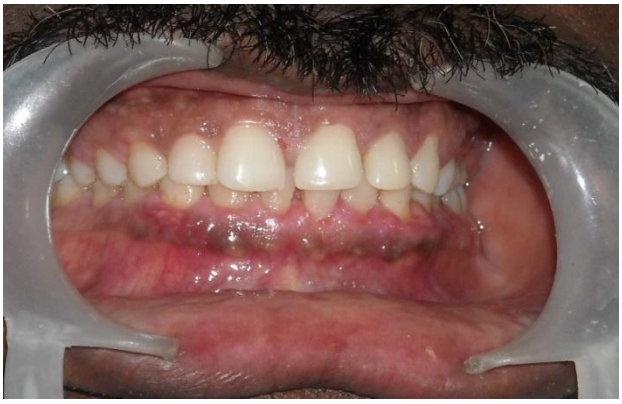

Figure 6: One week after gingivectomy

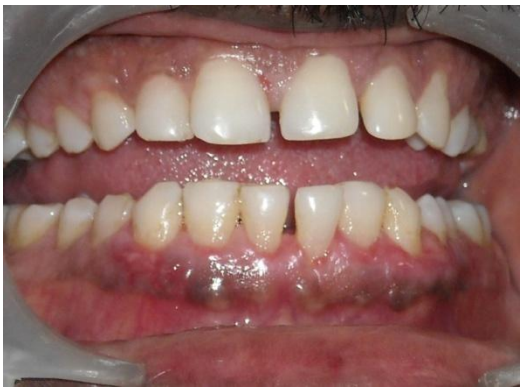

Figure 7: Six months post operative

RESULT AND DISCUSSION

Severe gingival overgrowth is often disfiguring and can interfere with both speech and mastication. Despite our greater understanding of the pathogenesis of DIGO, its treatment still remains a challenge for the periodontist. Management strategies can most simply be categorized as either non-surgical or surgical approaches. The primary aim of non-surgical approaches is to reduce the inflammatory component in the gingival tissues and thereby avoid the need for surgery [12]. Individual case reports have shown that meticulous self-administered oral hygiene, alongside professionally delivered oral hygiene and scaling and root planing can result in complete resolution of both cyclosporin [13] and nifedipine-induced gingival overgrowth [14]. However, it should be emphasized that these were only case reports and lacked controls. They do help to illustrate what can be achieved in certain patients by nonsurgical means. Although a variety of non-surgical measures have been shown to be of some value in the management of DIGO, surgical correction of gingival overgrowth is still the most frequent treatment. Such treatment is mostly indicated when overgrowth is severe. The use of clinical indices such as the gingival overgrowth index (Seymour et al [11]) in research have suggested that surgical intervention is warranted when scores in excess of 30% are apparent. However, in the day-to-

day management of individual patients it is perhaps more important to consider the impact that gingival changes may have on the patients quality of life or their ability to maintain a healthy periodontium. From the patient's prospective, surgical correction of DIGO should result in little or no post-operative pain or sequelae, good aesthetics and a reduced risk of recurrence. Currently, the surgical management of DIGO includes the scalpel gingivectomy, overgrowth flap surgery, electrosurgery and laser excision.

Histological examination reveals number of fibroblastic cells and connective tissue fibres in CsA-GO samples similar to non-inflamed healthy gingiva after professional supra- and sub-gingival debridement and plaque control [15]. There is enhanced fibroblast cellularity and thickening of the oral epithelium in CsA gingival enlargements [16, 17, 18]. Saito et al [19] reported an intense expression of Ki-antigen in fibroblasts of hyperplastic gingival tissues and an undetectable immunostaining in the controls. Studies reveal that CsA alone is not directly influencing the proliferation rate of fibroblasts, but rather acts through indirect networks via locally released inflammatory mediators or bacterial products [20, 21]. It has also been studied that numerous lymphokines exert direct fibrogenic action which can increase that induced by the drug [22]. Kantarci et al [23] proposed that the CsA-GO has two components: fibrotic enlargement of CsA origin and inflammatory lesions caused by microbial dental plaque.

The above findings suggest that if the management of DIGO is targeted at eliminating the overgrowth and suppressing the inflammation by good plaque control measures, stable results can be achieved without the need for drug substitution.

CONCLUSION:

The CsA Gingival Overgrowth is a multifactorial disease in which various factors may play a significant role and where many aspects of connective tissue homeostasis can serve as targets for inducing drug to cause overgrowth. The aim of the treatment is to reduce the inflammatory components in the gingival tissues and hopefully reduce the overgrowth to more aesthetically acceptable or manageable levels. Ideally, all patients about to be medicated with cyclosporin, phenytoin or a calcium channel blocker, should go through a full periodontal assessment and any disease presented treated appropriately. Unfortunately, for many of these patients this is impractical and such patients often present to the periodontist with existing gingival overgrowth. For many patients, surgery is the main option and the scalpel gingivectomy is still the treatment of choice.

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