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Cyclosporin A-Induced Gingival Hyperplasia in Psoriasis: Review of the Literature and Case Reports

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SUMMARY Cyslosporin A (CyA) treatment of psoriasis is warranted in severe cases where other, conventional antipsoriatic approaches have failed. Gingival hyperplasia is a rare side effect of cyclosporin A treatment in psoriasis patients. Previous studies in cyclosporin A-treated patients (mostly transplant recipients) have demonstrated correlation between cyclosporin A serum levels and oral hygiene status on the one hand, and the prevalence and severity of this overgrowth on the other hand. Severe cases of gingival overgrowth may call for radical treatments such as periodontal surgery. Our aim was to present a severe form of cyclosporin A-induced hyperplasia in two female patients and to give an overview of the current literature on the issue. High serum levels of cyclosporin A were observed in both patients. Moreover, high initial plaque accumulation was noted in both patients. Upon cessation of drug administration and a combined periodontal treatment, virtually complete reduction of the gingival enlargement and inflammation was observed. Consequently, early diagnosis and an all-inclusive treatment of cyclosporin A-induced hyperplasia can result in virtually complete remission of the symptoms and eliminate the need of aggressive treatments such as periodontal surgery.

KEY WORDS: psoriasis; cyclosporin A; gingival hyperplasia

INTRODUCTION

Cyclosporin A (CyA) is a hydrophobic, cyclic polypeptide derived from the fungus *Tolypocladium inflatum Gams*. Early investigations showed the drug to have a potent inhibitory effect on lymphocyte proliferation (1-3), specifically acting on the T cell response, with little, if any, action on the B cells (3-6), without being cytotoxic or myelosuppressive at the same time (7). For that reason, CyA is a key drug used for immunosuppression necessary for the prevention of transplant rejection. Moreover, CyA has also tremendous therapeutic value in the treatment of disorders where aberrant immunoregulation is considered to be an etiologic factor, such as type I (insulin dependent) diabetes, systemic lupus erythematosus, polymyositis, acute dermatomyositis, Crohn's disease, ocular Behçet's syndrome, endogenous uveitis, psoriasis, atopic dermatitis, rheumatoid arthritis, and pemphigus vulgaris (3,8), just to name a few.

CyA is a potent immunosuppressor because it interferes with the activation of the cytotoxic and helper T cells, thereby impeding the immune response. Cytokines, soluble factors secreted by lymphocytes and monocytes, regulate the immune

response to infection, cancer, and transplanted organs. CyA blocks transcription of genes involved in T lymphocyte activation by inhibiting calcineurin phosphatase, an intracellular signaling pathway that regulates the expression of cytokines. Specifically, activated calcineurin is responsible for nuclear translocation of the transcription factor-cytoplasmic nuclear factor of activated T cells (NFAT). The orchestrated activation of NFAT and other transcription factors allows for the expression of cytokines such as interleukin (IL)-4, IL-2, and interferon (IFN)-γ, among others (9-14). Since IL-4, IL-2, and IFN-γ are important for the activation of both type 2 and type 1 helper T cells, respectively, CyA shuts down the cellular branch of the immune system. Thus, CyA prevents the generation of mature T helper cells (13-16), without an inhibitory effect on previously activated cytotoxic cells (17) or T-suppressor cells.

CyA is usually administered orally. The oral therapeutic dose for immunosuppression is 10 to 20 mg/kg body weight/day, which results in a serum concentration of 100 to 400 ng/ml (18), and plasma half life of 17 to 40 hours (19,20). Extensive metabolism of CyA in the liver results in at least 12 metabolites, which have minimal immunosuppressive properties (21,22).

The most common adverse effect of CyA is a decreased glomerular filtration rate (23-25), which is initially largely asymptomatic. The most visible side effect of CyA therapy is gingival hyperplasia (GH). It is of no surprise, therefore, that it was among the first reported side effects of CyA (26-28). In most cases, gingival overgrowth occurs within 3 months of CyA treatment. The prevalence of CyA-induced gingival overgrowth is extremely variable (27%-81%) (29,30), which is most likely due to drug dosage, duration of therapy, method of assessment of gingival overgrowth, and the medical condition for which the drug was being used.

CyA-induced gingival overgrowth starts as a papillary enlargement which is more pronounced on the labial aspects of the gingival mucosa and in-between the teeth (interdental papillae area) than on the palatal or lingual surfaces. Over time, the papillary enlargements increase in size and coalesce with each other, making the gingivae hard, swollen, rounded and lobulated. Overgrowth is largely limited to the width of the gingivae, although it can extend coronally and interfere with the occlusion, mastication and speech. The hyperplastic gingival tissues are often highly inflamed, bleeding readily on probing.

The relation between CyA dosage and degree of gingival hypertrophy has been subject to debate. Some studies have shown that gingival overgrowth is related to high doses of CyA in the plasma or saliva, or later stages of the CyA regimen (31-36). The presence of dental plaque increases the likelihood of gingival hyperplasia in CyA-treated patients, as it may provide a reservoir for the accumulation of CyA (33,36-38). No association between sex or age has been shown for development of gingival hyperplasia in response to CyA therapy (36,38,39). It has been postulated that HLA-DR1 is protective, while other HLA types correlate with increased susceptibility to gingival hyperplasia in response to CyA (39-42). Interestingly, however, high degree of HLA-A mismatching between the host and donor might be protective for GH development in renal transplant recipients on CyA therapy (38).

Histologically, it is not known for sure if CyA-induced gingival hyperplasia is a true hyperplasia because enlargement may not result simply from an increase in the number of cells but from the increase in extracellular tissue volume. The overlying epithelium is of variable thickness, irregular, and multilayered, with acanthosis, parakeratosis and pseudoepitheliomatous proliferation. The epithelial ridges penetrate deep into the subepithelial connective tissue. Microscopic examination shows sparsely vascular fibrous connective tissue with thick, dense, interlacing bundles of collagen fibers with an inflammatory infiltrate, primarily plasma cells. CyA is known to increase the level of collagen in the gingival tissue by inducing collagen production (43,44), and by inhibiting the degradation of collagen by gingival fibroblasts (45,46). After all, IL-1 has been known for long time to induce the production of collagenase (47), which normally degrades collagen, and CyA indirectly reduces the levels of IL-1 secreted by monocytes, which, in turn, could explain the accumulation of collagen in the gingivae in patients taking CyA. CyA also lowers free cytosolic calcium levels (48,49), which, in turn, can impair extracellular collagen degradation and increase noncollagenous secretions by fibroblasts (50). However, in addition to the increase of collagen synthesis, there are reports on a decrease in protein/collagen synthesis (51,52) as well as on a failure to alter protein synthesis (53,54). Another complicating factor is that CyA has also been observed to increase the levels of noncollagenous matrix (55).

CyA is also known to have fibroblast proliferation properties, and there have been indications

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that changes in fibroblast cell density occur as the lesion progresses (50,56). However, some reports claim that there are no changes of the cell proliferation rates in hyperplastic lesions (51,52). These seemingly contradictory findings could potentially be due to the fibroblast heterogeneity in each of these studies. After all, the actual scenario may in fact be an all-inclusive one that takes into account many of the different results.

Treatment of gingival overgrowth in CyA-treated patients has usually focused on maintenance of strict oral hygiene together with scaling and root planing, or attempting to replace CyA with another drug whenever possible. If these two approaches fail, a more aggressive treatment is warranted, such as periodontal surgery.

So far, CyA-induced gingival outgrowth has been mainly described in organ transplanted patients. However, CyA is also effective in the treatment of severe psoriasis (57-60). Psoriasis is a chronic autoimmune skin disease induced by autoreactive IFN-γ producing T helper cell (Th) 1 lymphocytes which orchestrate other cellular reactions, resulting in hyperproliferation of keratinocytes (acanthosis), concomitant inflammation, and dermal proliferation of small vessels (61-63). Given that CyA inhibits T cell function, it is a logical choice from an efficacy standpoint in the treatment of psoriasis. After all, rapid improvements in the prognosis have been observed in psoriasis patients treated with CyA at 2.5-5.0 mg/kg/day. In what seems to be the most comprehensive study on the side effects of CyA treatment in psoriasis patients, gingival enlargements were observed in only 19 (mere 4.3%) out of 422 patients participating in the study (64), which is well in accordance with other reported studies (60,65), but still significantly lower than that observed in CyA treatment of transplant recipients (29,30). As such, gingival enlargement is a rare side effect of CyA therapy during the treatment of psoriasis.

Two cases are presented of severe and rare CyA-induced gingival outgrowth in two female patients who were treated for an aggressive form of psoriasis.

CASE REPORTS

Two female patients aged 45 and 52, suffering from severe and resistant forms of psoriasis (erythrodermica/arthropathica), presented to Department of Dermatology, Skopje University Hospital Center in Skopje, Republic of Macedonia. Many treatment modalities (topical steroids, calcipotriol, phototherapy with UVB, photochemotherapy (PUVA) and PUVA-retinoids (re-PUVA)) were tried in the patients. Since they did not respond sufficiently to these conventional therapeutic measures, and moreover, phototherapy and chronic exposure to photochemotherapy implies an increased risk of photocarcinogenicity, a systemic approach with CyA was undertaken. The patients had no personal or family history of any conditions that may be exacerbated by CyA, including but not limited to hypertension, renal disease, cancer, migraine, and vascular disease (66,67). They were initially treated with CyA at a mean dosage of 2.7 mg/kg/day for 6 weeks, with some favorable response. Plasma CyA levels reached 310 and 290 ng/ml for the two patients in that period. On oral examination, the gingivae were significantly enlarged by the end of the first 6 weeks of CyA treatment, but did not interfere with any normal function. CyA therapy was continued for a total of 6 months with gradual dose reduction until complete discontinuation of the medication. During the following period, gradual worsening of the gingival condition was observed. Specifically, the gingivae were so enlarged that most of the patients' teeth were covered by tissue overgrowth (Fig. 1). The most affected regions were the interproximal papillae in the anterior segments of the jaw, incisors and canine teeth, particularly their labial (vestibular) surfaces. Moreover, the gingival enlargement was accompanied by severe inflammation, constant pain and spontaneous gingival bleeding. An abundance of plaque was found surrounding the enlarged tissue.

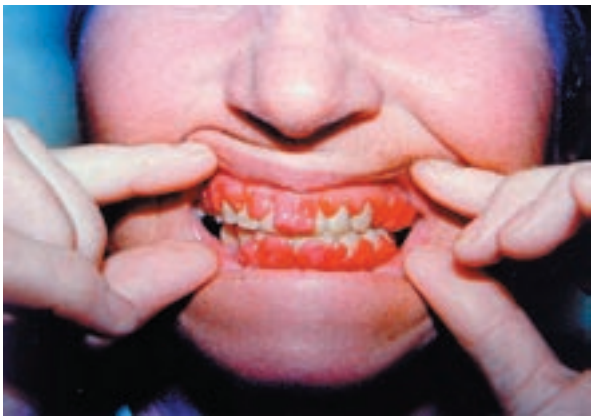

Figure 1. Marked gingival hyperplasia due to cyclosporin A.

The patients received detailed oral hygiene instructions at the beginning of treatment; however, they complied poorly with these instructions. Upon worsening of the gingival enlargements, the

patients were instructed to undergo professional periodontal treatment. Scaling and root planing under local anesthesia were performed in order to significantly improve their oral hygiene. Within a month of periodontal treatment, visible reduction in the gingival overgrowth and inflammation was achieved.

No other adverse events in response to CyA therapy were reported. No renal dysfunction, hypertension, infections or malignancies were observed in these patients while on CyA treatment or during the 6-month follow-up. No abnormalities in the electrolyte panel, renal state (calcium, phosphate, magnesium, blood urea nitrogen, and two baseline measurements of serum creatinine), uric acid, liver function tests, cholesterol, triglycerides and complete blood count were recorded.

Erythrodermic and arthropathic psoriasis responded only moderately to this CyA regimen. At the end of CyA therapy, remission of the gingival changes to normal was achieved. Similarly, during the 6-month follow-up, the gingival enlargements disappeared completely, with little residual gingival inflammation.

DISCUSSION

Psoriasis is a complex disease. First, the simple manifestation of psoriasis requires genetic predisposition towards abnormal keratinocyte proliferation and differentiation. In addition, the appearance of psoriasis needs an initiating event that involves a potent proinflammatory cocktail of cytokines resulting in hyperproliferation of keratinocytes, concomitant inflammation, and dermal proliferation of small vessels (61-63). Therefore, blocking the aberrant inflammatory environment in the affected areas improves prognosis. CyA is a potent inhibitor of the immune response (13-16), and as such a good candidate for the management of psoriasis in cases where other treatments have failed. However, CyA is associated with a significant incidence of side effects, such as gingival hyperplasia. The severity of this side effect has been correlated with high serum and/or saliva levels of CyA (31-36), and the presence of dental plaque (33,36-38). Our patients had serum levels of 310 and 290 ng/ml, which were at the high end of normally observed CyA serum levels of 100 to 400 ng/ml (18). More important, our patients had a significant plaque accumulation at the beginning of treatment. The management of plaque accumulation proved to be crucial in reducing the CyA-induced enlargements since the first reductions in the overgrowths were observed after the recommended periodontal treatments during CyA therapy. The end of CyA treatment marked an even more rapid reduction of the gingival inflammation and enlargements.

To sum up, two uncommonly severe cases of CyA-induced hyperplasia in two psoriasis patients are presented, accompanied by a discussion on the etiology of this rare scenario. In addition, this report introduces an effective therapy involving reduction of dental plaque levels in both patients in a timely manner as a way to reduce gingival enlargements in CyA-treated psoriasis patients with almost no longterm side effects, thereby eliminating the need of more invasive approaches, such as periodontal surgery/gingivectomy.

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