CyClosporine-induced gingival overgrowth in renal transplant recipients

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Abstract

Gingival overgrowth is one of the most frequent side effects of immunosuppressive therapy with cyclosporine A in renal transplant patients. The exact pathogenesis of this pathology is uncertain but several influencing factors have been hypothesized such as age, gender, genetic predisposition, oral hygiene status, pharmacokinetic variables, immunological changes and concomitant use of other medications. Current treatment options for this pathology include conservative measures (plaque control, oral hygiene improvement, drug replacement) associated or not with surgical therapy. The oral specialist plays an integral role on the transplant team in establishing a clinical protocol that assists the organ transplant recipient in maintaining optimal oral health.

Key words: gingival overgrowth, cyclosporine, transplant

Introduction

Over the past years, renal transplantation has become a successful treatment method that improves the quality of life of thousands of patients who suffered of end stage kidney disease. Between 2012-2017, 1440 kidney transplantations took place in Romania and the number is growing [1]. Moreover, as medical science progresses and the life expectancy of transplant recipients increases, the number of the patients who will seek dental care also increases. Since all transplant patients need immunosuppressive rejection-preventive drugs after surgery (usually a combination of calcineurin inhibitor, glucocorticoid and azathioprine/mycophenolate), they are also more susceptible to the development of systemic complications [2]. Lesions in the oral cavity may arise as a result of immunosuppression or drug interactions [3,4]. Among these, drug-induced gingival overgrowth, fungal infection or viral stomatitis caused by herpes simplex virus, varicella zoster virus, cytomegalovirus and Epstein Barr virus associated or not with hairy leukoplakia, has frequently been reported [5-8]. Lip and oral cancer are also described, as well as oral ulcerations and oral lichenoid reactions [9,10].

Gingival overgrowth (GO) is one of the adverse effects induced by calcineurin inhibitors such as cyclosporine A [11]. This side effect is not only aesthetically unpleasant but also impairs nutrition and access for oral hygiene, resulting in increased susceptibility to oral infections, caries and periodontal disease. It has also been associated with other medication such as antiepileptic drugs or calcium channel blockers [12,13].

Prevalence and pathogenesis

Cyclosporine A (CsA), a cyclic polypeptide of 11 amino-acids derived from Tolypocladium Inflatum Gams, is an immunosuppressive drug widely used to
prevent graft rejection after organ transplantation and to treat several autoimmune disorders such as rheumatoid arthritis, psoriasis and Behcet’s disease [14,15]. Its clinical use is often associated with side effects which include hepatotoxicity, neurotoxicity, hypertension and gingival overgrowth affecting both the epithelial and sub-epithelial components to varying degrees [16]. Drug-induced gingival enlargement has a wide prevalence rate, 13-81%, which could be related to other risk factors influencing the development of this adverse effect such as age, gender, genetic predisposition, oral hygiene status, pharmacokinetic variables, immunological changes and concomitant use of other medications [17-20]. However, the exact mechanism underlying the pathogenesis of gingival overgrowth is still unclear.

Frequently, the development of this lesion occurs in the first 4-6 months after transplantation due to the high dosage of the immunosuppressant drugs, and usually affects the anterior teeth of both maxilla and the mandible. Studies show that the prevalence of gingival hyperplasia is three times more common in men as well as in younger age groups [4,21,22]. This fact could be due to a stronger inflammatory response, poor oral hygiene and hormonal imbalance in renal transplant recipients [23]. Also, CsA dosage and treatment duration have been proposed to influence the prevalence rate of GO [24]. Thus, it was shown that a daily dose of 500 mg was associated with the development of hyperplasia and the effect of this drug was reversible when the medication was discontinued [25]. Furthermore, Guleck et al found that longer duration of CsA use positively correlates with this lesion [26].

Nephrotoxicity is a serious side effect of cyclosporine therapy that appears to be caused by arteriolar vasoconstriction due to local release of thromboxane Calcium-channel blockers (CCB) have the capacity to interfere with renal vasoconstriction caused by cyclosporine and by this mechanism might minimize cyclosporine nephrotoxicity. Therefore, many renal transplant recipients require antihypertensive treatment [27]. The combination therapy of CsA and CCB (nifedipine, amlodipine) showed a significantly higher incidence of GO than when CsA is used alone [28-30]. The CsA-amlodipine association exhibits lower gingival enlargement and severity than CsA-nifedipine association [30,31].

The clinical observations of the pathogenesis of CsA-induced gingival hyperplasia indicate a potential role of periodontal bacteria. It is not clear whether accumulation of dental plaque is a consequence of gingival changes caused by the drug itself, or it is an essential factor for initiating the pathogenesis [25]. Many authors believe that inflammation is responsible for gingival enlargement which could be prevented by proper plaque removal [11,32-35]. Despite this association, it has been reported that GO can occur in patients with good oral hygiene or, by contrast, can be absent in patients with heavy amounts of plaque, which might be explained by genetic and susceptibility factors [32].

Gingival immune inflammation has been characterized as well as a risk factor and cytokines play an essential role in the regulation of the type of the immune response [17,36]. Previous studies have demonstrated significant increased levels of pro-inflammatory cytokines (IL-1, IL-6, transforming growth factor beta and plateleterived growth factor) which were shown to play a pivotal role in the development of cyclosporine-induced GO [37,38].
studies reported that cyclosporine increases the rate of human fibroblast proliferation in vitro [37,39] and that increased level in keratinocyte growth factor receptor is consistent with the increase in proliferation rate of epithelial cells observed in CsA-induced gingival hyperplasia [40]. On the other hand, it was also reported that cyclosporine increases the production of cellular matrix, collagen, interleukin 6 (IL-6) and the variations in the balance between cell proliferation and apoptosis could contribute to the etiology of GO [39].

CLINICAL AND HISTOLOGICAL FEATURES
Drug-induced GO begins as an enlargement of the papillary gingiva, which is more pronounced on the labial surfaces and less orally. Although the overgrowth is usually restricted to the keratinized gingiva, in severe cases it can completely cover the crowns of the teeth, interfering with speech and mastication [41]. Gingival enlargement can also complicate the patient’s oral hygiene and the patients’ ability to clean the teeth, thus increasing the inflammatory process and in return further increasing the gingival overgrowth. Hyperplastic tissue bleeds on periodontal probing and it is more susceptible to infection. Also, it is absent in edentulous areas and will disappear in areas where teeth are extracted [11].

The appearance of gingival overgrowth in patients on CsA varies slightly and presents a more vascularized, lobulated and inflamed gingiva in comparison with a more fibrotic and uniform growth found in association with other medication [11]. The histopathology shows hyperplasia of the gingival epithelium or expansion of the connected tissue with increased collagen production or a combination of these [42]. CsA-induced GO shows less fibrosis, increased inflammation and increased cellular infiltrate in the connective tissue as compared to GO caused by other drugs [39].

PREVENTION AND TREATMENT
Dental plaque has been suggested a causative cofactor of gingival enlargement. There are reports that poor oral hygiene exacerbates drug-induced GO and that oral hygiene measures may reduce the degree of growth but they do not inhibit its development [43,44]. As the first step in the prevention of drug-induced GO, optimal plaque control and frequent periodontal maintenance (once every 3 months) are required [43]. Each recall appointment should include detailed oral hygiene instructions and thorough prophylaxis with supra and subgingival calculus removal as needed. Topical anti-inflammatory agents are usually successful in providing symptomatic relief [45]. Chlorhexidine mouthwash in concentrations of 0.2% to 0.12% is considered the gold standard in preventing plaque accumulation [46,47]. Mild gingival enlargement will often diminish with removal of plaque and calculus deposits. Even moderate gingival enlargement may reduce enough to avoid surgical intervention. While excellent oral hygiene and professional plaque control can potentially prevent or lessen the severity of the condition, they are often insufficient for reversing the process once it is established [43] One treatment option includes withdrawal of CsA and conversion to Tacrolimus, together with an extensive plaque control program which could be an effective and safe alternative to reduce GO severity in a short period of time, although the reduction is not that evident in cases with concomitant use of calcium channel blockers. [27]. Even though some authors recommend the substitution of CsA by Tacrolimus to reduce the incidence and the
severity of gingival growth, this therapy is not always efficient, since GO induced by CsA may persist after changing drugs. Furthermore, Tacrolimus is involved as well in the development of gingival hyperplasia, but less frequently [17,20].

Some authors studied the effect of the administration of Azithromycin (250-500 mg/per day for 3-5 days) which resulted in significant regression or inhibition of CsA-induced GO in renal transplanted patients, for a period of 3 months to 2 years [48]. The mechanism by which Azithromycin may decrease GO is unknown. Some authors have suggested that Azithromycin may improve CsA-induced GO by blocking CsA-induced cell proliferation and collagen synthesis, and by activating MMP-2 in gingival fibroblasts with CsA-induced GO [49]. In a recent review, authors have explained the triple action of Azithromycin, namely, antibiotic, immunomodulator, and anti-inflammatory effect, which makes it a useful drug, especially for periodontium [50].

In severe gingival enlargement, which consequently may cause functional and esthetical problems, surgical gingival excision is indicated, but the recurrence is frequent (40% of cases within 18 months), especially when oral hygiene is not properly maintained [17]. Surgical interventions include gingivectomies and/or laser excision therapy [11]. The clinical advantages provided by laser assisted surgery include mainly reduction of bleeding, absence of oedema, a higher comfort for the patient and a much more rapid healing [51, 52]. The use of electrocautery and carbon dioxide lasers has shown some utility for reducing gingival enlargement, an approach which provides rapid postoperative haemostasis [53]. No matter what surgical technique is chosen, consultation with the patient’s nephrologist prior to surgical treatment regarding antibiotic and steroid coverage should take place. Professional debridement with scaling and root planning as needed has been shown to offer some relief in gingival overgrowth patients.

The demand for complex oral rehabilitation has significantly increased in the late decade due to the high aesthetic demands of patients [54]. Treatment planning becomes more complex where there is periodontitis associated with gingival enlargement, which poses a cosmetic or functional problem. Easy diagnosis of periodontal disease and the identification of patients at risk is a current challenge for clinicians [55]. Periodontitis alone can be treated using conventional clinical care, but when associated with the gingival enlargement, may require periodontal surgery: pocket elimination along with removal of excess tissue, or a combination of the two [11]. Since a bidirectional relationship exists between periodontal disease and chronic renal failure, chronic inflammation, and cardiovascular risk, it is reasonable to increase the efforts to prevent, diagnose, and treat periodontal disease [56,57]. On the other hand, inflammation plays a critical role in organ transplant rejection. Therefore, periodontal disease can have serious effects on the long-term post-transplantation success [56].

For patients with end-stage renal disease, kidney transplantation is the best treatment option. Long-term survival and quality of life of renal transplant recipients has become a major focus of post-transplantation patient care and includes prevention of cardiovascular complications, diabetes mellitus and bone metabolism disorders which persist few years after transplantation [58,59,60].
CONCLUSIONS

Gingival enlargement is a side effect of the long-term administration of cyclosporine and it seems that bacterial plaque plays a pivotal role in the development of the overgrowth. Therefore, optimal plaque control and periodic periodontal maintenance are required. Surgical treatment to excise and remodel the gingival contour should be considered whenever gingival overgrowth causes aesthetic and functional problems. A collaborative care which integrates various disciplines and team members responsible for the patient’s health should be approached. The oral specialist plays an integral role on the transplant team in establishing a clinical protocol that assists the organ transplant recipient in maintaining optimal oral health.

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