

CYCLOSPORINE INDUCED GINGIVAL HYPERPLASIA IN KIDNEY TRANSPLANT: A CASE REPORT AND REVIEW OF THE LITERATURE

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Abstract

Kidney transplantation is considered the best therapeutic option for end stage renal disease (ESRD). Cyclosporine is a potent immunosuppressive drug used to prevent graft rejection. Gingival hyperplasia is one of the collateral effect of cyclosporine, the exact pathogenesis of cyclosporine induced gingival hyperplasia is uncertain, and it may interfere with normal oral functions causing unpleasant appearance, carry psychological impacts and leads to difficulty in maintaining good oral hygiene. A 28 year old male patient reported to the department of Oral Medicine of the School of dentistry, University of Sulaimani, he had renal transplantation and he is on long term immunospressive drug (cyclosporine), the patient complains of gingival swelling, intraoral examination revealed severe generalized gingival hyperplasia, periodic oral examination of kidney transplant patients who are on long term cyclosporine drug treatment is important to monitor any signs of gingival hyperplasia, reassurance and management based on general medical condition of the patient.

Keyword: Kidney transplantation, cyclosporine, gingival hyperplasia

Introduction

Kidney transplant (KT) is the most efficient renal replacement therapy for a significant number of patients with ESRD (1). Survival of KT patients has increased because of improvements in candidates selection and study process, surgical techniques, immunosuppressive drugs and protocols, and a better surveillance and management of extra-renal risk factors. Cyclosporin-A (CsA) is a drug used to prevent rejection of the kidney graft. It is a cyclic polypeptide calcineurin inhibitor. Its administration prevents the expression of genes for several cytokines whose activity is critical for lymphocyte T activation, including interleukins 2 and 4, gamma interferon, tumor necrosis factor α and others, thus preventing lymphocyte proliferation. The drug is used either alone or combined with other immunosuppressor drugs (2). Its use causes collateral effects, such as nephrotoxicity, hirsutism, arterial hypertension, dermatosis (2,3) and lymphoproliferative diseases (3).

Gingival hyperlasia is a collateral effect of Cyclosporine A use. The variability of clinical expression of Cyclosporine A -related gingival hyperplasia implies a multifactorial pathogenesis. Cyclosporine A blood concentration, plaque/gingivitis level, bacterial lipopolysaccharides, and alteration of calcium ion cellular influx have been suggested as possible factors (4). Gingival hyperplasia may interfere with normal oral functions, leave patients with an unpleasant appearance, carry psychological impacts, influence compliance with medical therapy, and make it difficult to maintain optimal oral hygiene (5). The latter, in turn, may exacerbate GO via bacterial overgrowth (4). The immunosuppressive actions of Cyclosporine A may allow tissue invasion by micro-organisms, which causes a secondary inflammatory response (6).

We presented a case of cyclosporine induced gingival hyperplasia along with the review of the relevant literature

Case report

A 28 year old male patient attending the department of Oral Medicine of the School of dentistry, university of Sulaimani, he had renal transplantation and he is on long term immunospressive drug (cyclosporine) for prevention of rejection. This work was approved by the Committee of Ethics in Research of the University of Sulaimani. According to Declaration of Helsinki, signed consent form was obtained from the patient before conducting it. The patient was complained of gingival swelling, intraoral examination revealed severe generalized gingival hyperplasia (Figure 1). The patient was assured about the cause of his problem as it is related to long term cyclosporine immunosuppressive treatment and treated by gingivectomy.



Figure 1: Cyclosporine-induced gingival hyperplasia in 28 year-old male renal transplanted patient

Discussion

Cyclosporin A (CsA) is a powerful immunosuppressant widely used for prevention of transplant rejection as well as for management of a number of autoimmune conditions such as rheumatoid arthritis (7). CsA 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 (8).

The major adverse reactions to cyclosporine therapy are nephrotoxicity, hepatotoxicity, tremors, hirsutism, hypertension, mild anemia, gingival overgrowth and, in rare instances, lymphoma (9). The drug-induced gingival enlargement is a side effect of some immunosuppressive drugs such as cyclosporine A, which is the drug of choice in kidney transplant patients (10). Cyclosporin-induced gingival overgrowth is more common in pediatric organ transplant patients (52%) as compared to adults (11), males were at greater risk from developing gingival overgrowth than females (11).

The precise mechanism of cyclosporine-induced gingival overgrowth is uncertain. Various investigations for pathogenesis of gingival overgrowth support the hypothesis that it is multifactorial (12). Overgrowth in cyclosporine-treated patients is dependent upon the interaction of several factors. These include plaque control, the level of gingival inflammation and

extent of periodontal destruction; the dosage and duration of cyclosporine therapy; plasma and tissue concentrations of the drug and metabolites; age of the patient and perhaps the underlying medical condition (13).

Cyclosporine-induced gingival overgrowth commences as a papillary enlargement which is more pronounced on the labial aspects of the gingiva than the palatal or lingual surfaces (14). 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. Cyclosporine induced gingival overgrowth has not been reported in edentulous subjects (15). 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. (16) One of the foundations of all drug induced gingival overgrowth is drug substitution, reduction in the dose of cyclosporine has been shown to be beneficial, (17), however the nature of organ transplant often means that alternative therapy or dose reduction is not available. Some patients can use more conventional immunosuppressant such as steroid and azathioprine but survival rate are not as good new immunosuppressant such as tacrolimus (FK 506) (Prograf), rapamycin and mycophenolate mofetil (MMF) Cell Cept may offer some hope, as to date these have not been reported in association with gingival overgrowth. It should be remembered that the condition for which patient are taking these drug can be very difficult to control and physicians may be very reluctant to modify an effective drug regime "just for gums" Thus, while it is worth asking if drug substitution is possible, the dentist should understand that a negative response is not necessarily a disregard for the gingival problem, but rather a concern for the debilitating effects of the underlying condition. Although the role of plaque has not been clearly defined in most medication induced gingival overgrowth, there is no doubt that the resulting gingival inflammation can contribute an additional level of enlargement due to oedema, regardless of any initiating or contributing effect it may have on gingival growth. Control of this inflammatory component of gingival overgrowth, while important in itself, also aid in determining if surgical reduction is necessary and, additionally, allows for a less hemorrhagic field in any subsequent surgical intervention (18)

A program of intense oral hygiene failed to prevent the onset of Cs-induced gingival overgrowth and it was not particularly effective at reducing overgrowth (15), but it was of some benefit for general periodontal health, as expected . Furthermore chlohexidine (0.12 percent) mouth rinse has been reported to reverse recurrent Cs overgrowth following gingivectomy (19)

Surgery is normally performed for cosmetic/ aesthetic needs before any functional need is manifested. In cases where drug therapy is likely to continue for many years, psychosocial consideration need to be considered in an effort to reduce the frequency and the extend of any surgical intervention. While classical external bevel gingivectomy is still a viable treatment option, the large denuded connective tissue wound that result can be painful and requires careful postoperative care to prevent infection. There is a tendency towards the use of either a total or partial internal bevel gingivectomy approach. This technically more demanding approach have the benefit of allowing 'primary closure' thus reducing the chance of post operative complications, however it requires more time and skill to a accomplish. Surgical treatment of PHT-, Cs and CCB-induced gingival overgrowth has centered on gingivectomy by conventional methods and, more recently by the use of CO2 lasers (20). The CO2 laser has been advocated because of the decreased surgical time, rapid postoperative hemostasis and the fact that often the underlying medical conditions are relative contraindications for conventional surgery.

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