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Non-surgical treatment of gingival overgrowth induced by cyclosporin: a case report

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Gingival overgrowth induced by cyclosporin is frequently treated surgically. A case report of gingival overgrowth induced by cyclosporin associated with severe chronic periodontitis is described. This clinical case report describes an impressively positive treatment response following non-surgical periodontal therapy.

A 47-year-old male, with a generalised gingival overgrowth associated with tooth migration, large overjet and tooth mobility was treated. The medical history revealed a renal transplant, hypertensive state, and a family history of periodontitis. The patient was under a regimen of 200 mg cyclosporin and 100 mg captopril daily. The diagnosis was severe chronic periodontitis. Probing pocket depths of ≥ 8 mm were found in all teeth present. Treatment consisted in non-surgical therapy and reduction of the cyclosporin dosage. After 6 months of non-surgical treatment, clinical parameters demonstrated a great improvement with 90% of sites with 1–3 mm and 6% with 4–5 mm of probing depth, and absence of bleeding on probing. Tooth realignment and overjet reduction occurred spontaneously and the patient was totally satisfied with the treatment. Surgical corrections were not considered necessary. Supportive periodontal care was given every 3 months.

A cause-related approach working closely with the nephrologist could be adequate for treatment of cyclosporin-associated gingival overgrowth and periodontitis and should precede surgical treatment. The reduction in cyclosporin dosage may account for at least part of the obtained clinical results.

■ Introduction

Gingival enlargement may be associated with several stimuli, among them some drugs[1]. Cyclosporin, nifedipine and phenytoin are most commonly associated with gingival overgrowth.

Cyclosporin-A (CsA) is a hydrophobic, cyclic polypeptide containing 11 amino acid units[2]. It has been used in organ transplant patients to prevent rejection, and is also used in the control of several diseases such as Behcet's disease, Crohn's disease, rheumatoid arthritis, ulcerative colitis, pemphigus,

psoriasis and other several auto-immune skin diseases[2]. Among the main adverse effects associated with the use of CsA are nephrotoxicity, hepatotoxicity and hypertension. Hirsutism and gingival overgrowth are also found in cyclosporin users[3]. Since nephrotoxicity and hypertension may occur, patients often also use calcium channel blockers like nifedipine, which epidemiological data has associated with gingival overgrowth[4].

The prevalence of gingival overgrowth varies between 25% and 81% in CsA users[2,5,6] and it is likely that several risk factors are involved. Variation in individual susceptibility can be a result of dosage, duration of CsA treatment, concomitant use of other drugs, age, gender, genetic factors, immunological changes, systemic diseases and periodontal conditions such as level of dental plaque control, gingival inflammation and pre-transplant enlargement[6-10]. Histologically, areas with clinical gingival overgrowth demonstrate low to moderate hyperkeratosis, increased stratum spinosum layer, connective tissue fibrosis, fibroblast proliferation, increased number of capillaries with chronic perivascular inflammation and basal layer of the epithelium projected into the connective tissue[11,12]. There is disagreement about whether gingival enlargement reflects a true increase in numbers of fibroblasts[2]. Wysocki et al[13] described increased numbers of fibroblasts within the gingival connective tissue. In contrast, Pisanthy et al[14] demonstrated that gingival enlargement may result from an accumulation of non-collagenous extracellular material and a thickening of the epithelium. These contrasting findings may be due to differences in the evolutionary stage of the overgrowth[2]. CsA's main effect as an immunosuppressive agent is to suppress the production and function of the T lymphocytes, particularly T helper cells. It has little effect on the B cell system and decreases the humoral response to the nonmitogenic T-dependent antigens[15].

Clinically, gingival overgrowth associated with CsA is similar to that linked to nifedipine. However, tissue flaccidity and haemorrhagic tendency are frequent. These characteristics are a function of the inflammatory pattern[16]. The lesions are more often found in proximal areas, especially from the buccal aspect[1,6]. Plaque and gingival bleeding are also common[4,10].

Among a series of problems associated with gingival overgrowth, the most important are phonetic alterations, masticatory problems, tooth migration, plaque retention and aesthetic impairment[2,17]. Thus, emotional and social problems may arise, leading to depression, frustration and anxiety[18].

The importance of the bacterial biofilm in the pathogenesis of gingival overgrowth has been studied extensively. However, no clear correlation between plaque-induced gingival inflammation and development of CsA-mediated gingival overgrowth has been established[19-21]. Clinical and epidemiological studies have found associations between levels of plaque control and the prevalence/severity of gingival overgrowth[3,5,6,10,21]. However, these findings are from cross-sectional studies and causality cannot be established. On the other hand, in spite of the high plaque scores, little evidence exists in humans about loss of attachment/bone or tooth loss in these patients.

There is no consensus on the effects of home and professional plaque control on gingival enlargement. Several authors have observed a positive association between an intensive oral hygiene programme, supra- and sub-gingival scaling, and improvement of CsA gingival overgrowth[22-24], while others failed to confirm this[25-27]. Ideally, all patients who are going to be medicated with CsA should go through a full periodontal assessment and any disease presented should be treated properly to reduce inflammatory components in the gingival tissue. Unfortunately, such patients often present to the periodontist with existing gingival overgrowth[28]. Thus, treatment approaches are determined by the severity of gingival overgrowth. In initial cases, non-surgical periodontal therapy is indicated[17,18,23]. In severe cases, surgical tissue removal is used[28]. However, recurrence is common[27,29]. Whenever possible, a review of the drug prescription should be considered[30,31].

Few reports on the effect of non-surgical periodontal therapy in severe cases of gingival overgrowth have been published. Hancock and Swan[32] and Ciantar[33] described cases of significant reduction and control of nifedipine-induced gingival overgrowth by thorough scaling and root planing with meticulous plaque control. However, the gold standard still seems to be the surgical approach[17,26,28,29,34]. Hence there are some reports describing CsA-associated gingival overgrowth and severe periodontitis. The present case reports the treatment of a patient with CsA-associated gingival overgrowth and severe periodontitis by means of a non-surgical approach.

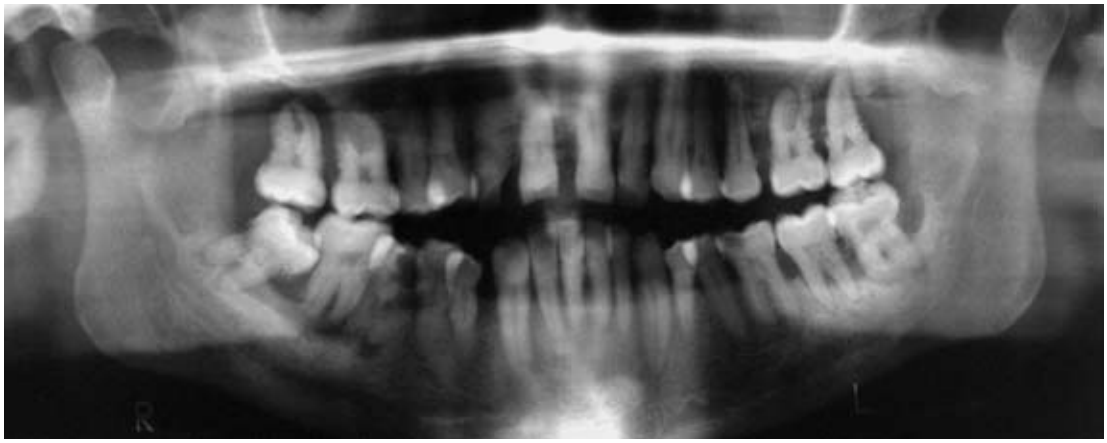

Fig 1 Orthopantomogram of the patient, showing large amount of bone loss.

■ Case description and results

A 47-year-old male, with gingival overgrowth associated with aesthetic problems, chewing difficulties and oral malodour, was referred to a periodontist. Important medical history findings included a renal transplant 16 years prior to consultation, as well as a hypertensive state. The patient had been taking CsA 200 mg once daily and captopril 50 mg twice daily since the transplant. A family history of periodontitis was also reported. The patient avoided smiling. Gingival overgrowth was present in all segments of the mouth, associated with tooth migration, a large overjet and tooth mobility. When asked about when the gingival enlargement started to appear, the patient answered that it had been present for a few years, but could not remember the exact date. However, the patient was certain that gingival enlargement started after the use of CsA. No other risk factors were identified. Visible plaque was present at roughly all surfaces (4 sites assessed for each tooth), 60% of them associated with calculus. Marginal gingival bleeding (4 sites for each tooth) was present at 100% of tooth surfaces. Probing pocket depths of ≥ 8 mm were found in all teeth present (probing of 6 sites for each tooth). Clinical attachment level could not be measured reliably due to the overgrowth and the large amount of calculus. However, the orthopantomogram revealed advanced generalised bone loss (Fig 1).

A diagnosis of gingival overgrowth associated with CsA as well as generalised severe chronic periodontitis was made. The treatment strategy included communication with the nephrologist to assess the possibility of reviewing the prescription. The physician then prescribed Micophenolate 360 mg twice daily and reduced the CsA dosage to 25 mg/day.

Before the first intervention, the nephrologist was consulted regarding antibiotic prophylaxis, with antibiotic prophylaxis recommendations given. Periodontal therapy was performed in a two-step approach: supragingival plaque control, followed by subgingival scaling and root planing. Supragingival plaque control was performed by removal of plaque retentive factors (including supragingival calculus), and oral hygiene instruction using a multi-tufted toothbrush, and dental floss with 1% chlorhexidine gel. Nine teeth (17, 16, 26, 27, 38, 37, 48, 47 and 46) were extracted due to advanced bone loss. After two sessions of supragingival plaque control, reduction of the oedema was achieved. Non-surgical scaling and root planing under local anaesthesia was performed once a week for one month. No intentional removal of soft tissue was performed during scaling and root planing. Subgingival curettage was not performed and granulation tissue was not removed.

Thirty days after the last scaling and root planing session, re-evaluation took place and since clinical parameters had shown a great improvement, surgery

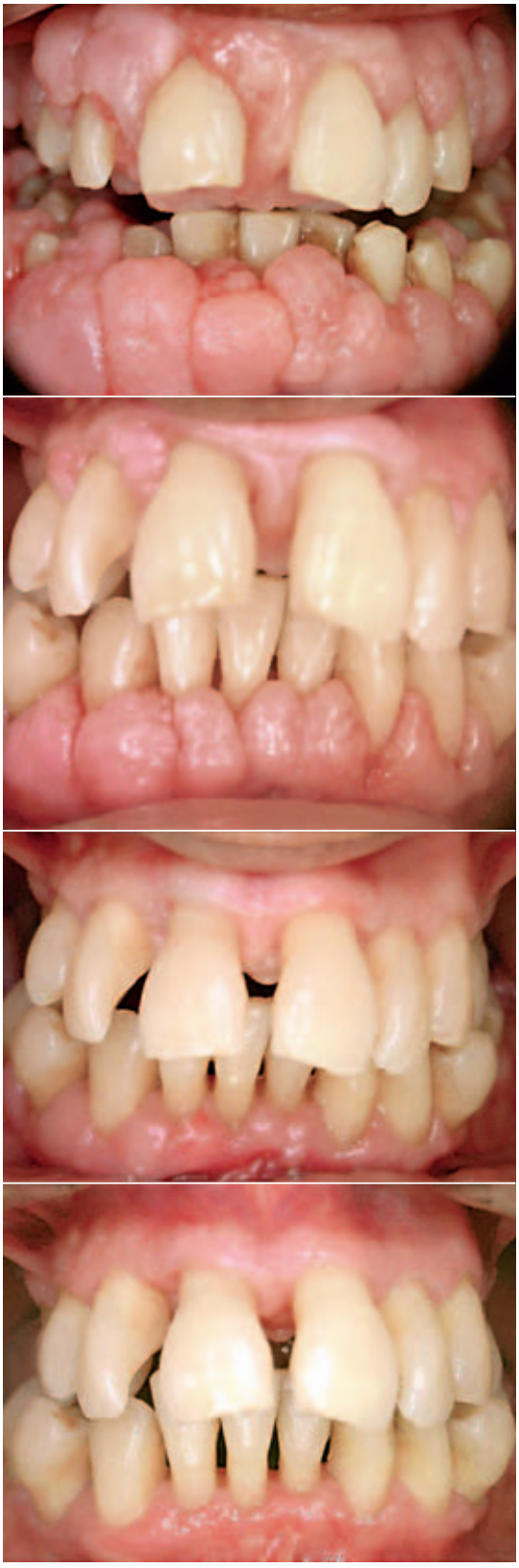

Fig 2 Labial view of the gingival changes before treatment, 1, 3 and 12 months after non-surgical treatment respectively.

was not considered necessary. At this moment, 90% of sites were 1–3 mm deep and 6% were 4–5 mm deep. Although clinical attachment levels had not been measured at first examination, a gain in clinical attachment was observed, probably due to probing depth reduction. Hence, no bleeding on probing was detected. Tooth realignment and overjet reduction occurred spontaneously and the patient was satisfied with the treatment, particularly the reduced tooth mobility and enhanced chewing capacity. Supportive periodontal care was given every 3 months. Plaque and gingival marginal bleeding scores were below 10% of the surfaces in all evaluated periods, which confirmed the excellent plaque control by the patient. Figs 2 and 3 show the sequence of gingival changes pre-treatment and 1, 3 and 12 months after subgingival scaling and root planing.

■ Discussion

The present case report shows that a non-surgical approach may be considered the first choice even in advanced cases of gingival overgrowth. These findings are similar from investigations of Aimetti et al[35], who provided further evidence that plaque is important in the pathogenesis of CsA-induced gingival overgrowth. The authors demonstrated that proper self-performed supragingival plaque control combined with professional subgingival instrumentation is effective in the treatment of gingival enlargement in transplant patients medicated with CsA. At the end of the one-year period of observation, the gingival overgrowth score decreased by 1.82 from a baseline value of 2.38 in the anterior sextants and by 0.84 from a baseline score of 1.29 in posterior segments, according to Seymour's index[36].

Some investigators have suggested that oral hygiene is a routine approach to prevent or reduce gingival enlargement after transplantation[37,38,19], while others claimed that plaque control was effective only to a limited extent in the management of CsA gingival overgrowth. Seymour and Smith[25] used a plaque control programme and non-surgical approach as a means of treatment of CsA-induced gingival overgrowth. In their study, 27 adult renal transplant patients were randomly allocated after trans-

plant surgery to receive intensive oral hygiene instructions from a dental hygienist and scaling and root planing (OH group) or no treatment (no treatment group). Gingival condition was assessed 6 months after baseline and changes in gingival form were related to various periodontal and pharmacological approaches. In both treatment groups, there was a significant increase ($p < 0.05$) in gingival hyperplasia scores at 6 months. In the therapeutic approach of the present study, the patient was enrolled in a carefully supervised plaque control programme, with instruction, re-instruction, motivation and training by a periodontist. Also, 1% chlorhexidine gel was used as an adjunct. The use of chemical plaque control, despite the adverse effects, should not be overlooked[20]. It could be argued that in the present case a simplistic approach was adopted, with gingivectomy and oral hygiene instruction. However, considering the high rates of recurrence, associated in particular with less than optimal plaque control, it was in line with current understanding of the learning process that more time was allowed for knowledge to be absorbed and attitudes to change[29,39,40].

Revision or substitution of CsA dosage should be considered in the management of CsA-induced gingival overgrowth. Switching from CsA to tacrolimus resolved or improved CsA-related side effects, reducing the need for surgical interventions[41,42]. Also, the reduction in CsA dosage was intended to reduce occurrence of gingival overgrowth, due to the lower interference with the tissue metabolism[26]. The positive results of the present case report may be due to a combination of periodontal therapy and reduction of CsA dosage. This was a case of severe periodontitis with CsA-induced gingival overgrowth, and the positive results may in part be due to the combination of problems.

The remodelling of gingival tissues observed in the present case may be surprising; despite the apparent dense fibrotic tissue, removal of plaque and calculus allowed proper healing. Kantarci et al[24] investigated the 8-week clinical response of gingival overgrowth following non-surgical periodontal treatment and concluded that longer periods would be necessary to demonstrate significant improvement. In the present case, the most beneficial effects occurred within the first 4 months post-treatment, which includes the healing phase when the maturation of soft tissues occurs. The case was monitored

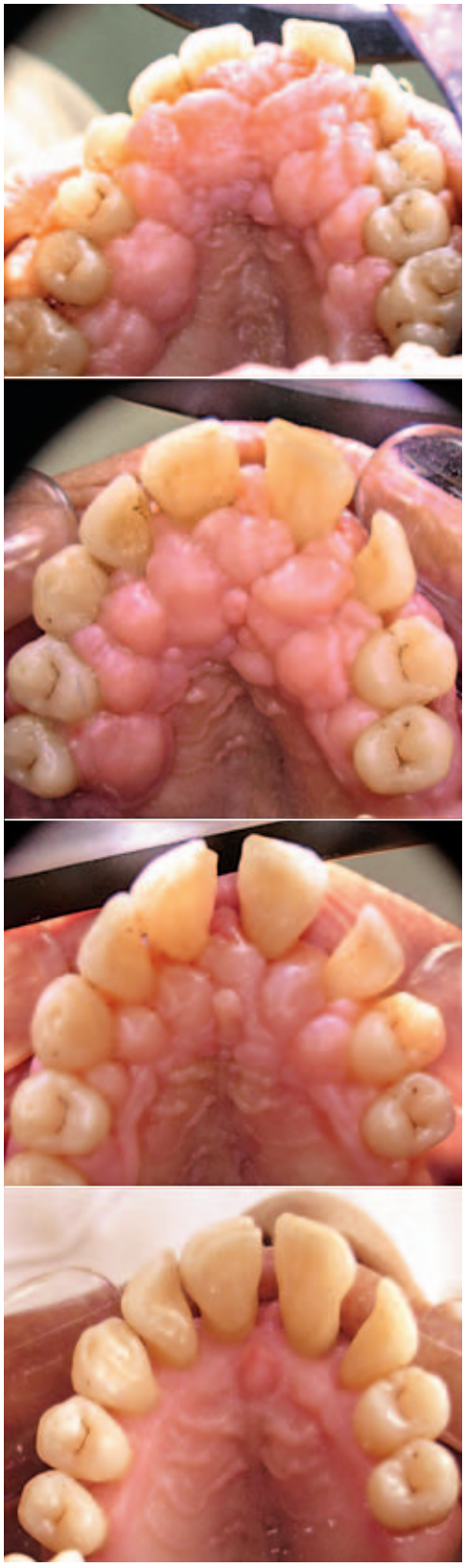

Fig 3 Palatal view of the gingival changes before treatment, 1, 3 and 12 months after non-surgical treatment respectively.

for several months and maintenance of the condition was observed.

CsA users do not have a higher prevalence and severity of attachment loss compared with controls[3,5,6,37]. However, the present patient presented severe attachment/bone loss. Owing to the unknown past periodontal history of the patient, the periodontal disease status before transplantation could not be ascertained. The family history of periodontitis may have influenced the disease status, and this led us to suspect that the case was not primarily a case of gingival overgrowth, but a case of severe periodontitis coupled with CsA-induced gingival overgrowth.

Fischer[43] evaluated the effect of CsA on the pattern of periodontal breakdown induced by ligature, using domestic ferrets as an experimental model. Although higher mean values of probing pocket depth were reported after 14 days in ferrets medicated with CsA, differences in probing attachment level in teeth with ligatures between the medicated and non-medicated animals after 28 days were not significant. The microbiological analysis showed differences in bacterial composition, with *Fusobacterium necrophorum* and *Eubacterium* species the major anaerobic bacteria in CsA-treated ferrets. Reasons for these differences are not completely understood. They may be related to changes in the immunological system, such as a decrease in T lymphocytes, changes in saliva and crevicular fluid composition, and/or the increased pocket depth in ferrets treated with CsA.

In treating gingival overgrowth, surgical approaches are most common. In the present case, periodontal therapy was performed non-surgically and without antibiotics. Recurrence of gingival overgrowth is high and may be independent of the type of treatment[26,29]. Gunsolley et al[44] found no differences between surgical and non-surgical approaches in severe periodontitis. Hence, these results can be maintained by supportive periodontal care[45].

■ Conclusions

From the clinical outcome of the present case, we conclude that a pathogenesis-related approach in conjunction with the nephrologist is adequate for treatment of CsA-associated gingival overgrowth and periodontitis. The reduction in CsA dosage may account for at least part of the obtained clinical results. In addition, non-surgical approaches are more conservative and may be more comfortable to the patients. Systematic intervention studies are therefore required.

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