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A case history of a kidney transplant patient with ciclosporin-induced gingival overgrowth combined with chronic periodontitis

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The exact patho-mechanisms of ciclosporin-induced gingival overgrowth remain unclear. Gingival hyperplasia is more severe in areas where local irritants such as plaque, calculus and defective restorations are present, although the role of dental plaque in the course of ciclosporin-induced gingival overgrowth is a matter of debate. A clinical case of a middle-aged kidney-transplanted woman is presented in which the gingival overgrowth was successfully eliminated by initial therapy and minimally invasive gingival corrective surgery. The patient's oral hygiene and periodontal health have been successfully controlled by regular supportive therapy for over 9 years.

■ Introduction

The first case of gingival overgrowth as a side effect associated with the administration of dilantin was reported by Kimball in 1939[1]. Currently, three major groups of drugs are responsible for the majority of gingival enlargements. Besides the dilantin group, calcium channel blocking drugs[2-4] and ciclosporin[2] can cause gingival overgrowth. The first case of ciclosporin A-related gingival hyperplasia was reported by Calne in 1981[5] and was followed by numerous case reports[6-8]. Ciclosporin A has mainly been used for preventing rejection phenomena following organ transplantation[5,9]. Ciclosporin is also used in the treatment of rheumatoid arthritis, multiple sclerosis, psoriasis, pemphigus vulgaris and other diseases of immunologic origin[10,11]. Ciclosporin specifically suppresses the function of some T as well as B lymphocyte subpopulations[12,13]. Ciclosporin can also exert direct effects on gingival fibroblasts. It stimulates production of connective tissue matrix macromolecules[14-16], and decreases fibroblasts' phagocytotic activity, leading to impaired collagen catabolism[17]. Ciclosporin may promote gingival overgrowth by causing altered production of certain cytokines and growth factors[18-22]. Lymphocytes andmacrophages

may also play an important role in this process[18,23]. Ciclosporin A has also been reported to inhibit bone resorption in organ cultures[24,25]. Ciclosporin-induced gingival overgrowth combined with tooth migration has also been reported in laboratory animals[26].

The incidence of ciclosporin-related gingival hyperplasia has been reported to vary between 10% and 70%[27]. Gingival hyperplasia is more severe in areas where local irritants are present[15,28-30]. The exact patho-mechanisms of the ciclosporin-induced gingival overgrowth are still unclear[31]. The role of dental plaque in the course of ciclosporin-induced gingival overgrowth is also a matter of debate. Dental plaque has been considered as an important risk factor for ciclosporin-induced gingival enlargement by many authors[32-35]. In laboratory animals, dental plaque retention appeared to be also a magnifying cofactor in the development of ciclosporin-related gingival overgrowth[36]. Nevertheless, many other reports found no correlation between dental plaque accumulation and the severity of ciclosporin A-induced gingival overgrowth[37-39].

The most frequently used treatment of ciclosporin-induced gingival hyperplasia is gingivectomy[40-43], but periodontal flap procedures offer much better post-operative plaque control and primary healing. Recurrence can occur after both gingivectomy and flap procedures[2,42].

A clinical case of a middle-aged kidney-transplanted woman is presented. She was followed up for approximately 9 years. The patient's gingival overgrowth combined with chronic periodontitis was successfully controlled after initial therapy by strict and effective homecare and regular professional supportive therapy.

■ Case report

In 1997, a 48-year-old woman was referred by her surgeon from the Department of Transplantology to the Department of Periodontology, Semmelweis University, Budapest, Hungary, with a chief complaint of severe gingival inflammation and enlargement. Her medical history showed that she had rheumatic fever with glomerulonephritis without any sign of endocarditis in 1955, when she was 6 years old. After that time, she always had problems with her kidney, and she was on a strict low-protein diet. The patient had never had any sign of heart murmur. By 1985, renal insufficiency developed, and regular, bi-weekly haemodialysis was required. After several months of dialysis treatment she received a kidney transplant, from her mother. After the kidney transplantation the patient received immunosuppressive treatment (a combination of ciclosporin A and corticosteroids). The transplanted kidney was functional for over 9 years but in 1994 her kidney had to be removed because of severe complications and rejection symptoms. She had another series of haemodialysis for over 6 months, until a compatible donor kidney was found from a brain-damaged individual. The second transplantation took place in 1995 at the Department of Transplantology, Semmelweis University, Budapest. Post-transplantation she also received immunosuppressive treatment, taking a combination of ciclosporin A and corticosteroids. Therefore she had been taking ciclosporin A for over 20 years. At this time she was receiving 250 mg ciclosporin A (Sandimmun, Novartis) and 4 mg methylprednisolone (Medrol, Pfizer) every day. With this combination of medication she had been under control for several years. Her renal functions were normal and her blood parameters and blood pressure were also within normal limits. The patient had been regularly monitored by the surgical team at the Department of Transplantology. During a recall visit, the patient's surgeon discovered pronounced gingival swellings and severe gingival inflammation in her mouth, and referred her for periodontal consultation.

■ Clinical findings

At admittance, intraoral examination revealed very severe gingival inflammation and gingival overgrowth both in the maxilla and the mandible (Fig 1a to 1c). The patient's oral hygiene was very poor; she had approximately 100% plaque score, and abundant supra and subgingival calculi were also present. The gingiva bled upon gentle probing all over. The gingiva exhibited severe enlargement, especially on the buccal aspects of the jaw bones. The gingiva was lobulated, and a soft, mulberry-like mass of tissue covered a relatively large area of the clinical crowns. Iatrogenic plaque retention factors were also present

(Fig 1b). She had several faulty fillings and crowns with overhanging, subgingival margins, and with broken acrylic facings. The attachment loss ranged from 3 to 6 mm and pocket depth ranged from 5 to 9 mm. The patient's maxillary and mandibular anterior teeth showed moderate mobility and tooth migration with marked opening of diastema (Fig 1c).

Prior to the start of periodontal treatment, the patient's surgeon was consulted and informed of the planned therapy. Her general physical condition did not contraindicate any invasive periodontal treatment. The patient had no heart murmur or other cardiac condition associated with regular antibiotic prophylaxis.

The goal of the initial treatment was to restore oral hygiene, remove plaque retention factors and control gingival inflammation to prepare the patient for gingival surgery. Initially, the patient received oral prophylaxis. Her supragingival plaque and calculus were removed with a Cavitron ultrasonic instrument. The patient received Clindamycin (600 mg per day) via oral administration for 10 days. Subsequently the overhanging fillings and crowns were corrected and the fillings polished. Thorough subgingival scaling and root planing was carried out in each quadrant under local anaesthesia (lidocaine with epinephrine 1:100.000 dilution). During these procedures, gentle subgingival curettage was also performed and the loose interdental grape-like lobulations were removed with Gracey curettes. Neither gingivectomy nor flap procedure were performed at this time. The ectopic left mandibular second premolar was extracted and the right mandibular four-unit bridge was removed. The patient received instructions regarding her brushing and flossing technique. Commercially available chlorhexidine (0.2 % Corsodyl, GlaxoSmithKline) solution was used to assist mechanical plaque control (Fig 2). After the completion of the initial phase of therapy, the patient was regularly checked and her individual oral hygiene was monitored. During the first follow-up period, the patient's oral hygiene significantly improved. At the beginning recalls were bi-weekly. Within 3 months the patient's plaque scores were under 20% and the bleeding sites were below 10%. The mass of the gingival tissue was significantly reduced. The mulberry-like surface of the attached gingiva smoothed and the pocket depth reduced (Fig 2). It was remarkable how the

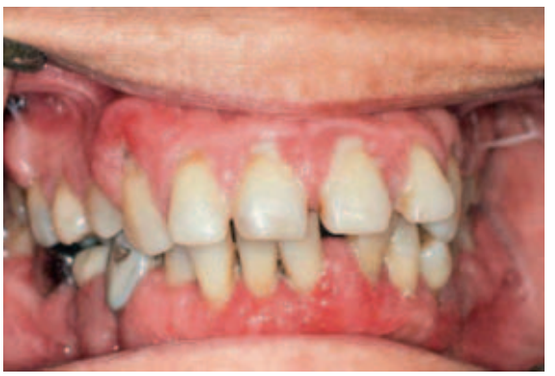

Fig 1a Pre-treatment photograph of a kidney transplant patient aged 47 at her first visit. She presented poor oral hygiene, severe gingival inflammation, massive gingival overgrowth, signs of clinical attachment loss and tooth migration.

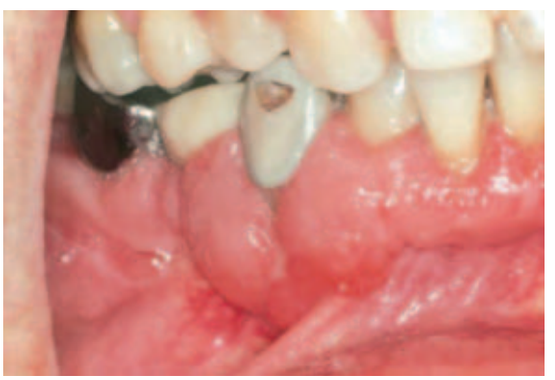

Fig 1b Iatrogenic plaque-retentive factors.

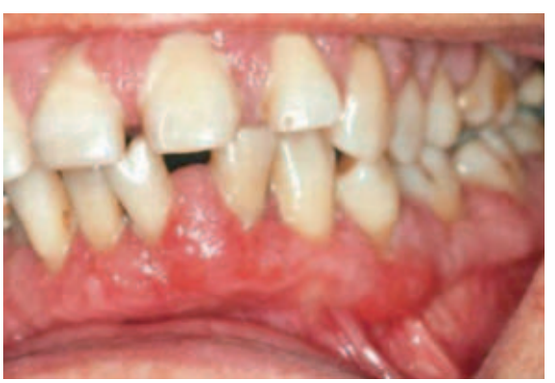

Fig 1c Anterior teeth with severe opening of diastemas.

wide diastema between the maxillary and mandibular incisors spontaneously closed without any orthodontic treatment during the initial phase of therapy (Fig 2). A metal-ceramic provisional bridge with supragingival margins was fabricated to replace the original bridgework (Fig 3). The patient's compliance was excellent and she performed efficient home care. Six months after her initial visit the gingival hyperplasia showed such a good healing tendency that the

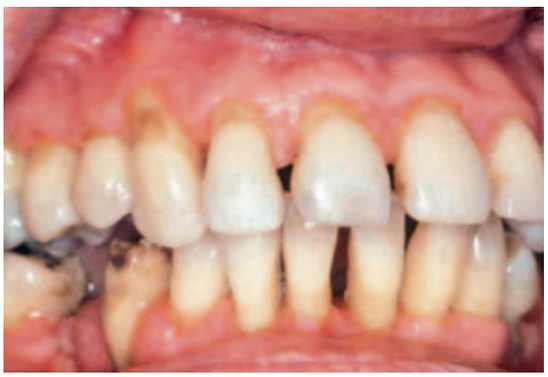

Fig 2 Clinical picture at the completion of the initial treatment phase. Note the patient's improved gingival and periodontal conditions and the tendency to spontaneous realignment of the anterior teeth and closure of the diastemas.

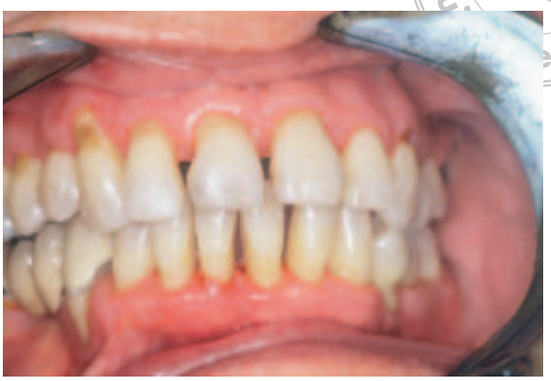

Fig 3 Two years later. Clinical view after the completion of patient's prosthodontic treatment.

initially planned gingivectomy was cancelled, and only minute flap procedures were carried out with internal bevelled incision to further reduce gingival mass and improve gingival contour.

Post-surgery, recall was bi-monthly for over 3 years. The provisional bridge was replaced with a new four-unit porcelain-fused-to-metal fixed restoration in 2001. The patient has since been on a regular 6-month recall. Her individual oral hygiene has been good and only minimal interdental plaque and calculus accumulation has been detected during recall visits. The gingival overgrowth receded completely. The shape, texture, contour and the colour of her gingiva was normal. The average clinical probing depth was 1 to 2 mm. The diastemas between the maxillary and mandibular anterior teeth closed completely and the tooth mobility decreased significantly. The patient fully appreciates her good oral health and maintains her 6-month recall programme (Fig 4a). The gingival recession finally ranged between 3 and 7 mm and no vertical bone loss has occurred (Fig 4b). The patient has been followed up for approximately 9 years, during which time she was still taking ciclosporin A and corticosteroids, but she did not experience any recurrence of gingival enlargement or active periodontal inflammation (Figs 5a to 5c).

■ Discussion

The relationship between dental plaque and drug-related gingival enlargement is still not well understood[32]. Many investigators have suggested a causal relationship between inflammation and gingival overgrowth. Since controversial results and cases have been reported, the role of dental plaque in the pathogenesis of ciclosporin-induced gingival enlargement is also a matter of debate. Several authors suggest that bad oral hygiene and increased plaque accumulation is rather the consequence and not the

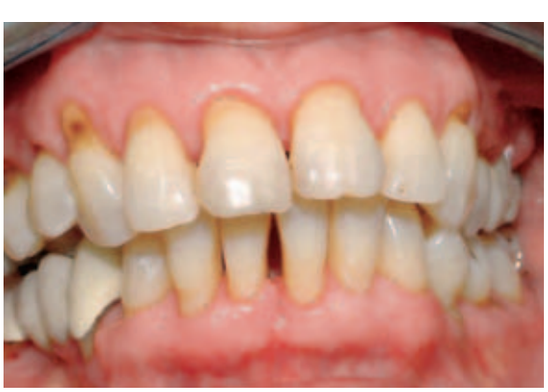

Fig 4a Five year follow-up. Note the complete spontaneous closure of the diastema between the anterior teeth.

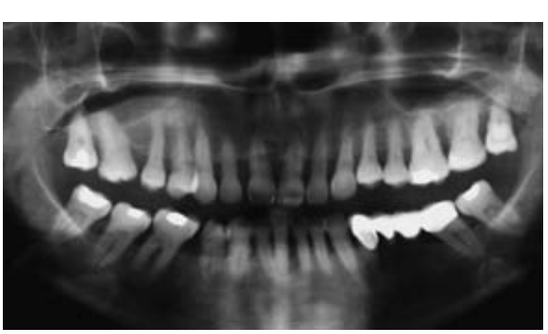

Fig 4b Panoramic radiographic status with an overall 30–40% horizontal alveolar bone loss but stable periodontal condition.

cause of gingival enlargement, as enlarged gingiva promotes plaque accumulation and hampers mechanical plaque control[37-39]. Longitudinal studies following up organ transplant patients showed that gingival overgrowth increased significantly while plaque and gingivitis scores decreased, owing to a strict post-operative oral hygiene programme[39]. On the other hand, several authors showed that if oral hygiene was restored and gingival inflammation reduced, gingival enlargement was also reduced[17,26,35,44]. Case reports have indicated that the use of chlorhexidine decreased the gingival overgrowth or anticipated the recurrence of gingival enlargement after surgical correction[45-47].

The role of dental plaque and gingival inflammation is also not clear in other drug-related gingival enlargements. It was reported that patients placed under strict plaque control simultaneously with the initiation of phenytoin therapy showed lower incidence and severity of gingival overgrowth[48,49]. It was also reported calcium cannel blocker-induced gingival overgrowth was reversed by meticulous oral hygiene[4].

In the present case report, a kidney transplant patient with chronic periodontitis combined with drug-induced gingival overgrowth was treated and followed up for approximately 9 years. Many case reports demonstrated clinical improvement after changing ciclosporin A to tacrolimus[50-52]. In the presented case the gingival and periodontal conditions showed continuing improvement over time due to the professional mechanical debridement and good individual oral hygiene, despite the continuous ciclosporin administration. After completion of the treatment phase the gingival enlargement did not recur during the maintenance phase; instead, further spontaneous gingival recession and maturation of the gingival connective tissue occurred. The spontaneous realignment and stabilisation of the maxillary and mandibular teeth without any orthodontic treatment might be attributed to the complete remission of the fibrotic overgrowth and the resolution of the active periodontal disease.

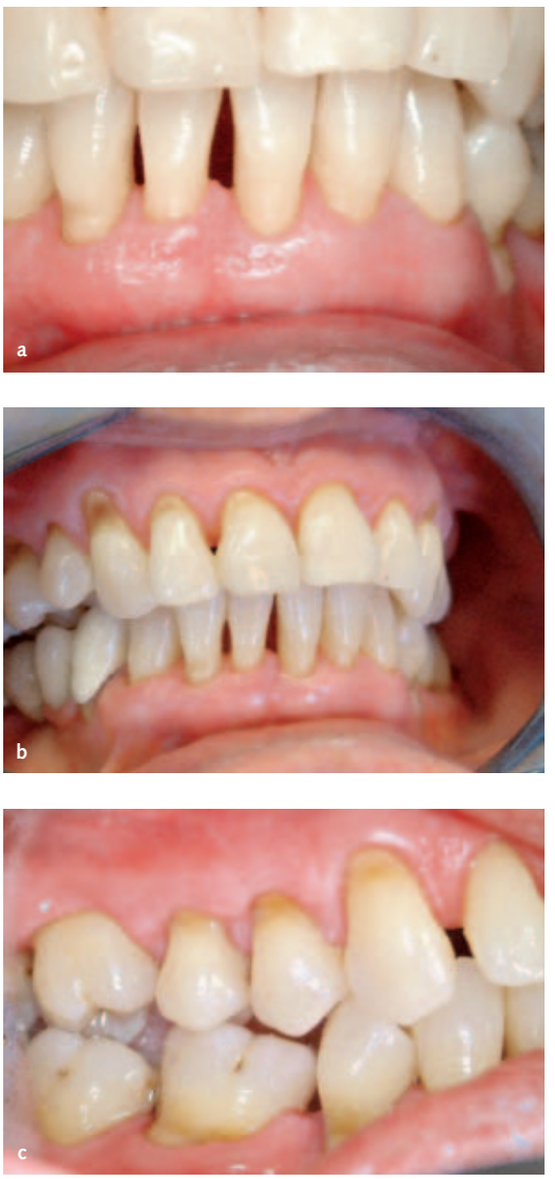

Fig 5a to 5c Photographic status 9 years after periodontal therapy. The photographs were taken 6 months after her last professional oral hygienic treatment just before professional cleaning. At the last recall, the patient presented a minimal amount of supragingival plaque and calculus and a stable gingival condition.

■ Conclusion

There is great individual variation in the susceptibility to drug-induced gingival overgrowth. Although many risk factors are listed in the literature, the exact aetiology and patho-mechanism of drug-induced gingival enlargement is still not clear. Many believe that dental plaque might be a decisive contributing factor in the development of drug-induced gingival overgrowth. The presented case might also support the view that meticulous plaque control should be one of the most important factors in the treatment and supportive therapy of drug-induced gingival overgrowth.

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