GINGIVAL OVERGROWTH INDUCED BY IMMUNOSUPPRESSIVE TREATMENT WITH CYCLOSPORINE A AND MYCOPHENOLATE MOFETIL IN A PATIENT WITH KIDNEY TRANSPLANT – A CASE REPORT AND LITERATURE REVIEW

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Abstract

Cyclosporine A, a drug that inhibits the immune response, has been widely used for over 30 years in immunosuppressive therapy protocols for patient-recipients of the transplanted organs. One of the commonly reported side effects of Cyclosporine A is gingival overgrowth, with varying degrees of severity, which may interfere with the aesthetics and normal functions of the oral cavity. Combination with other drugs that can recognize the gum tissue as a secondary target organ increases the risk of drug-induced gingival overgrowth. In cases where a lower dose of Cyclosporine A or conversion to another immunosuppressive agent (a drug not assigned to such a side effect) are not possible, the management of severe gingival overgrowth focuses on surgical excision of the excessively proliferated gingival tissue. We report the case of a young adult with moderate drug-induced gingival overgrowth, the beneficiary of a functional transplanted kidney about 9 years ago, treated with two immunosuppressives, who has undergone gingivectomy with electrocautery, as a necessary intervention to improve the oral hygiene and to avoid worsening of malfunctions in the oral cavity.

Keywords: *Cyclosporine A, kidney transplant, gingival overgrowth*

INTRODUCTION

Drug-induced gingival overgrowth is a known and unwanted side effect, connected with 3 groups of drugs: anticonvulsants, antihypertensives, such as calcium channel blockers, and immunosuppressives [1]. Cyclosporine A is the primary immunosuppressive drug used in the last 30 years in organ transplant medicine to prevent graft rejection by the host. The typical histopathological lesions observed in drug-induced gingival overgrowth are: increasing of the gum volume through an abnormal amount of connective tissue stroma with overproduction of collagen and other extracellular matrix proteins, plasma cell infiltration, increased number of inflammatory cells (macrophages), increased degree of vascularization cell, gum's covering by a parakeratinized epithelium with irregular extensions to depth [2]. Since rigorous oral hygiene measures were only intended to limit the constituted gingival overgrowth and not to prevent it, while substitution of the drug-regime is not always a viable solution for the effective control of the general status of a patient with organ transplant, surgery by gingivectomy represents the only therapeutic option for cases where severe gingival overgrowth interferes dangerously with the normal functions of the oral cavity.

CASE REPORT

A 29 year-old male patient was referred to the Clinics of Oral and Maxillofacial Surgery in Iasi for drug-induced gingival overgrowth, in June 2013 (fig. 1). At the age of 5 he was diagnosed with Alport syndrome or "hereditary nephritis" (a genetic glomerulonephropathy with progressive evolution to chronic renal failure, hearing loss and decreased visual acuity). Arriving in the end-stage of chronic renal failure (at the age of 18), he was the subject of a 2-year dialysis program, after which (in 2004), he received a kidney transplant (from a clinically dead donor). After the kidney transplant procedure, he followed a protocol of immunosuppressive therapy with Sandimmune^{R} (Cyclosporine A) and CellCept^{R} (Mycophenolate mofetil) (the treatment doses at

hospitalisation in our Clinics were: Sandimmune (50 mg), 2 cp per day and CellCept (250 mg), 6 cp per day). Since hypertension was secondarily diagnosed to nephropathy, he was treated for 2 years with Isoptin (240 mg), ½ tablet per day and Milurit, 100 mg per day. A few months after the initiation of immunosuppressive therapy, the patient noticed a moderate increase in the fixed gum dimensions (especially in the interdental papillae) for the frontal dental group, then for the lateral one, first on mandibula then on maxillary, without functional consequences (therefore, a total of 9 years for gingival overgrowth). In the last three months, he noticed an accelerated growth on the right side of the mandibular gingiva in relation to tooth 4.7 (4.7 tooth with stretched coronal destruction, grade III of abnormal tooth mobility and periradicular osteolysis visible on ortopantomography). The noticed gingival overgrowth interests both the vestibular and the lingual side of the mandibular arch, reaching the occlusal plane in the right side and covering 2/3 of crowns height for the rest of the dental arch. In the maxillary arch, gingival overgrowth interested especially the interdental papillae and the third of dental crowns height on the sides. Orthopantomography osteolysis revealed a discrete horizontal generalized osteolysis and a stretched periradicular osteolysis in tooth 4.7 (fig. 2). Blood biological explorations gave the following results: RBC = 3.72 (4.2-6x106/µL), Hb = 10.5 (13 to 17 g/dL), Ht = 32.6 (40-51%), serum urea = 68 (15-50 mg/dL), serum creatinine = 2.66 (0.7 to 1.2 mg/dL), serum total protein = 56 (64-83/g/L). The surgical treatment consisted of: 4.7 dental extraction, 2.7 dental extraction (otherwise unrecoverable), gingivectomy using the elecrocautery (both on the vestibular and oral side) for 4.8-3.3 dental group, with favorable postoperative evolution (fig. 3).

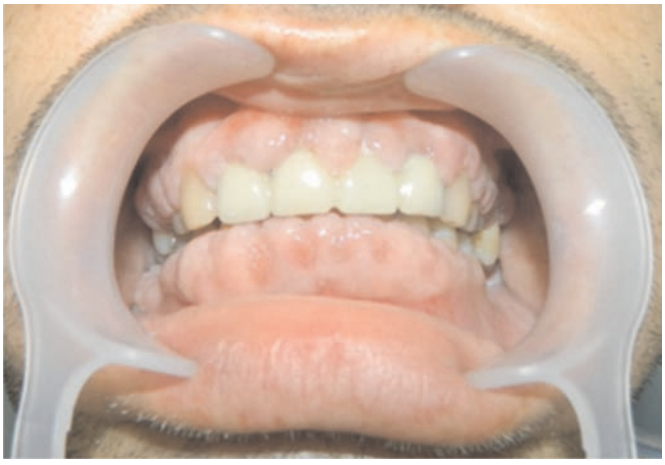

Fig. 1. Drug-induced gingival overgrowth (intraoral view at admission)

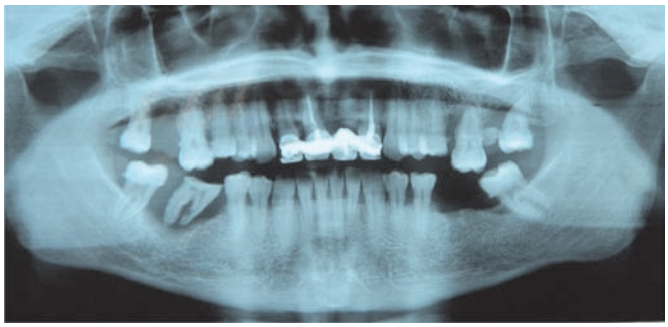

Fig. 2. Ortopantomography

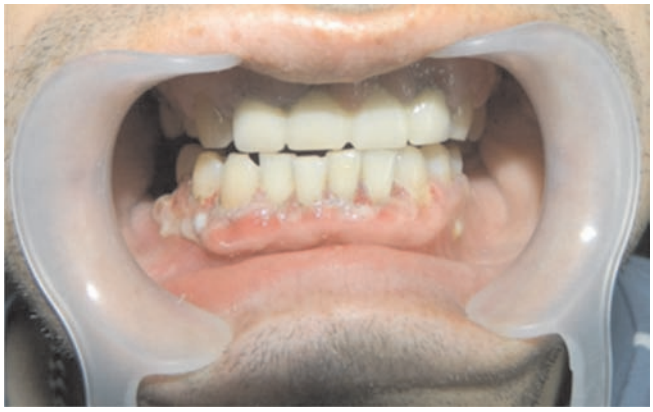

Fig. 3. Intraoral view 7 days after surgery (gingivectomy using the electrocautery)

DISCUSSION

In dentistry services, gingival overgrowth is one of the most common side effects seen in patients with renal transplant and immunosuppressive therapy with cyclosporine A [1].

Compared with the prevalence of gingival overgrowth in healthy population, estimated to be between 4 to 7.5%, the reported prevalence of gingival overgrowth detected after cyclosporine A therapy varies between 8-81% [2].

The now widely accepted term "gingival overgrowth" describes the excessive growth of the gum region, by increasing both the size

("hypertrophy") and number ("hyperplasia") of the cellular constituents [3]. As generally known, gingival overgrowth can be either hereditary or the result of some pathological reactions (leukemic infiltrates, granulomatous disease, Crohn's disease, sarcoidosis), or a secondary consequence of a chronic treatment with drugs from the following therapeutic classes: anticonvulsants (Phenytoin), antihypertensive – like calcium channel blockers type (Nifedipine, Verapamil, Diltiazem) and immunosuppressives (Cyclosporine A) [4]. Theoretically, the here presented case shows a greater risk of developing gingival overgrowth due to the treatment protocol, which included three absolutely necessary drugs (two immunosuppressives and a calcium channel blocker), known as inducing this side effect.

The immunosuppressive therapy is indicated in autoimmune diseases (psoriasis, systemic erythematosus lupus, rheumatoid arthritis, multiple sclerosis), but also to prevent rejection of the transplanted solid organ (kidney, liver, heart or other organs) [5]. Kidney transplantation (the most common transplanted organ), performed worldwide for about 60 years, is considered today to be a routine therapy for the management of irreversible renal failure, even if, after this procedure, it is mandatory to start the immunosuppressive therapy to create conditions for lymphocytic inactivity, thus avoiding rejection of the transplanted kidney [1].

Cyclosporine A was the first immunosuppressive drug used to prevent organ rejection and it is still the main immunosuppressive agent used for this purpose [6]. The clinical use of Cyclosporine A is often complicated by several well-documented side effects, including: nephrotoxicity, hepatotoxicity, neurotoxicity, diabetes, epilepsy, tremors, hypertension, gallbladder stones, hirsutism (hypertrichosis), impaired bone metabolism. Gingival overgrowth, the lingual fungiform papillae hipertrophy and hairy leukoplakia have been repeatedly reported in the oral cavity [7].

In gingival overgrowth, gum size may be affected in varying degrees (from mild to severe ones) so that, besides the aesthetic damage, this unwanted side effect of the immunosuppressive drugs may interfere with the normal functions of the oral cavity. Gingival overgrowth begins at the interdental papilla (especially in the anterior region, on the vestibular side), evolves symmetrically, limited to the fixed gum or gets extended to dental crowns, and can cause delayed eruption and/or ectopic teeth, dental malocclusions, speech disorders and, last but not least, difficulty in maintaining oral hygiene - leading to increased susceptibility to infections, cavities and periodontal diseases [8]. Gingival overgrowth has not been generally described in patients with edentulous or edentulous spaces, but sporadic reports of excessively increased gingival areas in edentulous patients with organ transplants were associated with microinjuries caused by removable dentures or Candida infections [1]. In the reported case, the proliferated gum size was moderate for jaw and severe for mandible (where it revealed certain areas of adjacent gingival inflammation and periodontal disease).

Cyclosporine A-induced gingival overgrowth has a multifactorial etiology, the risk factors incriminated for the increased incidence and severity of gum disease including: age at the time of transplant (inverse relationship), sex of the patient (men being three times more susceptible to this side effect), duration of treatment and dosage used (directly proportional relationship), drug concentration in serum and saliva, combination with other drugs (Cyclosporin A and Nifedipine combination significantly increases the incidence of gingival overgrowth), genetic predisposition and oral hygiene [1,2,9-11]. There is a wide (intra- and interindividual) variability in terms of susceptibility to Cyclosporine A-induced gingival overgrowth, this change being acknowledged, in principle, in over 70% of adult patients with organ transplantation, possibly even a few months after starting medication [12]. In this context, the reported case is distinguished by the following: hereditary kidney disease, kidney transplant performed at young age, immunosuppressive protection controlled by two drugs, hypertension secondarily to renal disease controlled by a drug with risk of gingival overgrowth, poor oral hygiene and consecutive periodontal disease, long-evolving gum proliferation.

Different therapeutic approaches have been proposed for the management of drug-induced

gingival overgrowth, such as: intensive oral hygiene programs, alternative pharmacological therapies and surgery to reduce the gingival size and reshape the gingival contour [1-3,6,8]. It is generally acknowledged that severe oral hygiene measures can reduce the established gingival overgrowth, even if they cannot stop its development, highlighting the role of dental plaque and gingival inflammation in initiating changes in drug-induced gingival overgrowth [8]. A decrease in the Cyclosporine A dose appeared as beneficial to gingival overgrowth, but, often, the nature of organ transplantation does not allow this course of treatment or an alternative drug therapy. In some selected cases (*e.g.*, if severe gingival overgrowth relapses after gingivectomy), an alternative to Cyclosporine A can be a new type of immunosuppressive drug: Tacrolimus (Prograf^{R}), Rapamycin, Mycophenolate mofetil (CellCept^{R}). Tacrolimus is an immunosuppressive with a different toxicity profile in comparison with Cyclosporine A and it is not associated with gingival overgrowth [13-18]. A severe gingival overgrowth, with aesthetic deficiencies involving or significantly interfering with the oral cavity functions (mastication, speech), brings into question excision of the gums grown in size (gingivectomy), a procedure that may appear as an inevitable choice, only after a thorough assessment (due to the risk of bleeding) [19]. The management in the reported case adopted a solution of necessity, caused by the impossibility of changing the treatment protocol, so that a gingivectomy with gingival contour restoration using electrocautery, for reducing to a minimum the risk of local bleeding, was performed.

CONCLUSIONS

Gingival overgrowth is a side effect of the long-term administration of immunosuppressives (Cyclosporine A and Mycophenolate mofetil) combined with calcium channel blockers (Isoptin), being also influenced by other risk factors (dental plaque and adjacent gingival inflammation).

Surgical excision of gingival overgrowth areas and gingival contour remodeling are required when this side effect causes aesthetic and functional impairments.

The gingivectomy performed with electrocautery is an effective method for removing the excessively increased gum, decreasing the risk of intraoperative bleeding.

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