

Phenytoin-Induced Gingival Overgrowth Management with Periodontal Treatment

Bruno César de Vasconcelos Gurgel, Carlos Roberto Batista de Morais, Pedro Carlos da Rocha-Neto, Euler Maciel Dantas, Leão Pereira Pinto, Antonio de Lisboa Lopes Costa

Department of Dentistry, UFRN - Federal University of Rio Grande do Norte, Natal, RN, Brazil

Correspondence: Dr. Bruno César de Vasconcelos Gurgel, Avenida Senador Salgado Filho, 1787, Lagoa Nova, 59056-000 Natal, RN, Brasil. Tel.: +55-84-3215-4103. e-mail: bcgurgel@yahoo.com.br

Phenytoin-induced gingival overgrowth (PIGO) is a common complication of the continuous use of medications. This paper presents a case of PIGO hindering oral function and compromising oral hygiene and aesthetics, which was treated with a combination of nonsurgical and surgical periodontal therapies. A 39-year-old male patient was referred for dental treatment with several complaints, especially upper and lower gingival overgrowth that hindered speech and swallowing. Generalized deep probing pockets and bone loss were detected. Diagnosis of gingival overgrowth associated with phenytoin and chronic periodontitis was established. The treatment plan consisted of conservative therapy with education on oral health, motivation and meticulous oral hygiene instruction in combination with scaling and root planing. During the reevaluation period, a marked reduction in the clinical parameters was noted, particularly probing pocket depth reduction. Surgical therapy for removal of gingival overgrowth was also performed to achieve pocket reduction. Supportive periodontal therapy was proposed and the patient is currently under follow-up for 4 years. Management of PIGO may be obtained by the use of periodontal procedures combined with good oral hygiene and periodontal supportive care.

Key words: phenytoin, gingival hyperplasia, periodontal therapy, plaque control, scaling and root planing.

Introduction

Drug-induced gingival overgrowth is a common complication of the continuous use of medications, such as anticonvulsant phenytoin, antihypertensive calcium channel blockers (nifedipine), and immunosuppressant cyclosporine-A therapy (1). Reports about the possible etiological mechanisms of drug-induced gingival overgrowth have been suggested (1-3) such as an imbalance in collagen synthesis and the degradation of gingival connective tissue, predominantly due to the inhibition of collagen phagocytosis of gingival fibroblasts (4). Additionally, cytokines and connective tissue growth factors could have an important role in gingival overgrowth (3). Deregulation of these balances could cause an abnormal differentiation of fibroblasts, resulting in their accumulation with proliferative and synthetic phenotypes (3, 4).

Phenytoin is a commonly prescribed medication for the treatment of patients with epilepsy. Kato et al. (5) have suggested that Phenytoin-induced gingival overgrowth (PIGO) was probably due to an imbalance in collagen degradation, rather than an increase in collagen synthesis. These authors demonstrated that the gingival fibroblasts demonstrate a specific extracellular matrix metabolism, stimulating, for example, prostaglandin E₂ (PGE₂) production and accumulation by gingival fibroblasts.

Kato et al. (5) showed a reduction in the expression of the genes encoding collagen types I and III in combination with a higher density of these fibers in gingival overgrowth; these authors suggested that PIGO was probably due to an imbalance in collagen degradation, rather than an increase in collagen synthesis. The same group of authors, in another study (6), also suggested a possible relationship between tumor necrosis factor - alpha (TNF- α) production and phenytoin in human gingival fibroblasts. Results suggested that TNF- α and phenytoin, together, caused impaired collagen metabolism as a consequence of enzymatic degradation by MMPs (matrix metalloproteinases)/TIMP-1 (tissue inhibitor of metalloproteinases) and integrin-mediated endocytosis, possibly leading to collagen accumulation during gingival overgrowth. Uzel et al. (7) also demonstrated that connective growth factors were elevated in phenytoin-induced gingival overgrowth, which characterizes a more fibrotic tissue.

It has been proposed that dental biofilm has an important role in the pathophysiology of gingival overgrowth and may be related to the risk and severity of this clinical manifestation (8,9). No specific group of bacteria seems to be specifically related to PIGO, in addition to those dental biofilm bacteria already implicated in periodontal disease (9). The host's response to pathogens associated with the biofilm may also play a role in PIGO. Host cell toll-like

receptors (TLRs) are cell membrane receptors that identify pathogen-associated molecular patterns (PAMPs), which are present on bacteria. Phenytoin may reduce the cell signaling of this process and may alter the inflammatory response in gingival tissues, favoring bacterial invasion and proliferation (10).

Excessive gingival overgrowth itself can also change the gingival contour, impeding oral function and speech and having an anti-aesthetic effect (3,11). Additionally, it can also compromise effective oral hygiene and may have negative implications for the systemic health of affected patients (3). Several approaches for the treatment of gingival overgrowth have been proposed (12-18): basic periodontal therapy, including oral hygiene instructions, prophylaxis, scaling and root planing, and continuous motivation as well as surgical therapy (gingivectomy or a flap procedure), antiseptic mouthwashes, and change of medication (3).

The aim of this report is to present a case of PIGO in a patient treated with nonsurgical and surgical periodontal

therapies with 4 years of follow-up.

Case Report

A Black 39-year-old male patient with gingival overgrowth was referred to the Department of Dentistry of the Federal University of Rio Grande do Norte, Brazil. The main complaints during this first appointment were halitosis, gingival bleeding and exaggerated upper and lower gingival overgrowth for a number of years. Significant medical history findings included epilepsy since the age of 15. The reported drug regimen was as follows: 300mg/day phenytoin and 100 mg/day phenobarbital.

Intraoral examination showed generalized edematous gingival tissue (Fig. 1A). During periodontal examination, high gingival bleeding index (80%) and a visible biofilm index (92%) were observed. Probing pocket depths ranged from 2 to 10 mm around most of the teeth, as well as large accumulation of subgingival calculus and supuration. Clinical attachment loss was observed in several teeth and bone loss was also confirmed by radiographic evaluation.

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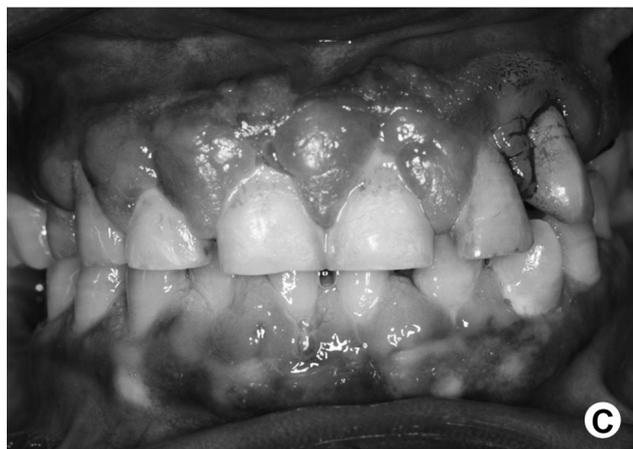


Figure 1. A: Buccal view before treatment. Intraoral examination showing generalized edematous gingival tissue. Note the upper and lower gingival overgrowth. B: Clinical aspect 3 months after first nonsurgical periodontal therapy. C: Clinical situation at 2 months after second nonsurgical periodontal therapy. Note marked reduction in gingival overgrowth. D: Four years of follow-up of surgical therapy by classic gingivectomy and gingivoplasty of upper and lower arches.

A diagnosis of gingival overgrowth associated with phenytoin and chronic periodontitis was made and no other risk factors were identified. The patient's physician was consulted in earlier appointments and medication could not be suspended or changed.

In view of this, the treatment plan consisted, initially, of conservative therapy with dental education, motivation and meticulous oral hygiene instruction, in combination with scaling and root planing and prophylaxis. The patient's mother, who cared for the patient, was instructed to aid the patient with effective oral hygiene, at least once a day. Additionally, a powered toothbrush was given to the patient, as well as a 0.12% chlorhexidine mouthwash to be applied twice a day during nonsurgical and surgical treatments.

The proposed therapy was found to be effective for improving the clinical parameters evaluated (gingival bleeding index and visible biofilm index were reduced to 34.7% and 30.5%, respectively), with marked reduction in probing pocket depth after two nonsurgical periodontal therapies.

At that time, reinforcement of attentive oral hygiene was performed and further scaling, root planing and prophylaxis were performed at sites that still presented bleeding on probing and subgingival calculus (Figs 1B and C). After, external gingivectomy was necessary in this case, based on oral function performance, and the individual esthetic concerns of the patient. Thus, surgical therapy consisted of upper and lower classic gingivectomy and gingivoplasty (external bevel incision) and surgical dressing application. Postoperative recommendations and medications were given as well as supportive periodontal therapy was proposed.

During the surgery, one gingival sample was removed

from the upper incisor after incision and immediately fixed in a buffered 10% formaldehyde solution. Semi-serial 6- μ m-thick histological sections were stained with hematoxylin and eosin and analyzed under light microscopy. In order to establish the presence of myofibroblasts in the gingival tissue, immunohistochemistry to detect the alpha-SMA (alpha-smooth muscle actin) antigen was also performed.

This report showed that clinical parameters revealed a considerable reduction in gingival overgrowth, after nonsurgical and surgical periodontal therapy. The maintenance therapy recall program has been effective because the patient is currently under follow up for 4 years of follow-up (Fig. 1D).

The histological diagnosis was compatible with drug-induced gingival hyperplasia (Fig. 2A). Microscopic analysis of the histological sections revealed gingival tissue fragments with an overlying surface of parakeratinized-stratified squamous epithelium exhibiting hyperplasia, acanthosis, spongiosis, hydropic degeneration, exocytosis and numerous and elongated projections (rete pegs) that protruded into the underlying connective tissue. In the underlying lamina propria, there was a dense fibrous connective tissue with an increased amount of collagen fibers, arranged randomly interspersed, and numerous spindle-shaped fibroblasts. Blood vessels of different calibers were also observed with some congested areas of intense and predominantly mononuclear inflammatory infiltrate, as well as areas of extravasated erythrocytes.

In order to establish the presence of myofibroblasts in the gingival tissue, immunohistochemistry was performed to detect the alpha-SMA (alpha-smooth muscle actin) antigen. Immunohistochemical analysis revealed that the

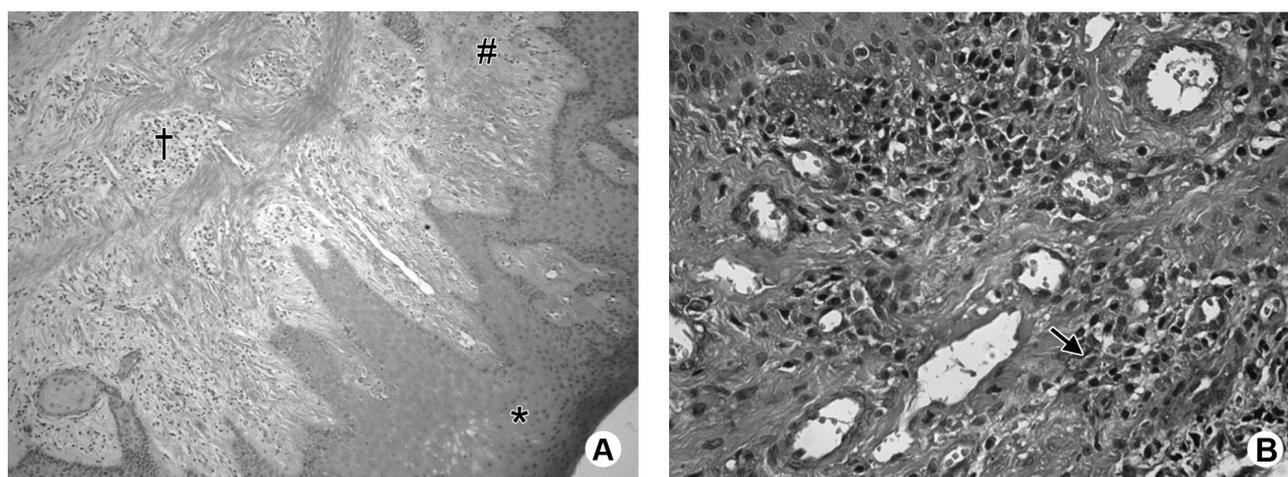


Figure 2. A: Histological section showing enlargement of the gingival epithelium (*) and dense fibrous connective tissue accumulation in lamina propria (#) in PIGO. It can be noted predominantly a mononuclear inflammatory infiltrate (†). Tissues were stained with hematoxylin and eosin (H/E). Light microscopy (100 \times magnification). B: Immunohistochemical analysis showing positive cell expression of α -SMA in the vascular smooth muscle cells and myofibroblasts (arrow) (400 \times magnification).

gingival tissue was positive for α -SMA in the vascular smooth muscle cells and in the myofibroblasts in the connective tissue (Fig. 2B).

Discussion

Gingival overgrowth is a fibrotic enlargement of the gingiva that can be caused by a variety of etiological factors. This disease may be exacerbated by dental biofilm and, sometimes, associated with other systemic diseases or occur as a side effect of systemic medications (3). Correa et al. (2) proposed that the mechanism of gingival overgrowth due to decreased collagen degradation may involve alterations in calcium metabolism, levels of MMPs and TIMPs and integrin expression. This fibrosis is characterized by the presence of numerous fibroblasts with an activated synthetic and proliferative phenotype that can be influenced by deregulated cytokines (3).

Phenytoin is a commonly prescribed medication for the treatment of patients with epilepsy due to its cost and familiarity and is not often substituted by other anti-epileptic drugs (2,11,19). However, the association with other drugs in the treatment of epileptic patients is also possible, such as phenobarbital, which could contribute to gingival overgrowth (1). Kamali et al. (19) were unable to determine whether concomitant medication of phenytoin with other anticonvulsants could lead to an increase in PIGO incidence during long-term therapy with phenytoin in epileptic patients. Moffitt et al. (16) suggested that other factors should be considered and investigated such as age, plaque control, pharmacokinetic variables, dosage, and duration of drug intake could be involved in the mechanism of gingival overgrowth.

Although the treatment of gingival overgrowth can be complicated due to the intense inflammation of the fibrotic tissue, the effect of periodontal treatment on gingival overgrowth was evaluated in this case report. Previous studies have shown that nonsurgical periodontal therapy, including supra- and sub-gingival tooth cleaning, may resolve or at least reduce the severity of drug-induced overgrowth and the need for surgical intervention (13,15-17). This report showed that clinical parameters revealed an improvement in manifestations with a considerable reduction in gingival overgrowth, after a number of appointments for scaling, root planing and oral hygiene instructions.

Surgical therapy was also decisive in improving the nonsurgical results achieved and for maintenance during this period of follow up. Mavrogiannis et al. (14) reported that PIGO could be managed by a variety of techniques (conventional gingivectomy, flap surgery and laser excision), however, they concluded that surgery remained the main option, with scalpel gingivectomy remaining as

the treatment of choice. It has been suggested (12,13) that patients with severe gingival overgrowth who require continuous drug therapy for medical reasons should undergo repeated surgical therapy periodically due to the recurrent nature of drug-induced gingival overgrowth. However, until the present moment, no additional surgical therapy was necessary for our patient.

It has been demonstrated that regular re-motivation and professional care after therapy are important to maintain long-term results (20). Ilgenli et al. (13) treated patients with nonsurgical and surgical periodontal therapy and a maintenance therapy recall program of 18 months. Using multiple regression analysis, the authors observed that age, gingival inflammation and attendance at recall appointments were significant determinants for gingival overgrowth recurrence. Additionally, Bharti and Bansal (22) proposed a decision-making protocol in the treatment of drug-induced gingival overgrowth starting at patients' first appointment until maintenance therapy.

Immunohistochemical analysis of the gingival tissue demonstrated the presence of myofibroblasts that could also be involved in gingival overgrowth. These mesenchymal cells present the characteristics of fibroblasts as well as those of vascular smooth muscle cells, which present a high expression of α -actin (α -SMA) (22,23). According to Dill and Iacopino (24), myofibroblasts are associated with the later stages of tissue turnover. Their presence in hyperplastic connective tissue from gingival overgrowth, induced by phenytoin treatment, suggests that phenytoin could exacerbate the normal tissue turnover/wound healing signals responsible for the presence of myofibroblasts. The mechanism that start gingival fibroblast transdifferentiation into myofibroblasts still remains unclear. However, it has been demonstrated an important participation of TGF- β in this process because it has a key role in regulating fibroblast proliferation and collagen synthesis (23,25). Therefore, further studies are important to clarify the pathogenic mechanisms of fibrosis in drug-induced gingival overgrowth.

It may be concluded that management of PIGO can be established with a combination of nonsurgical and surgical periodontal procedures. Additionally, the encouragement and maintenance of proper periodontal hygiene has an important and decisive role in its prevention.

Resumo

O crescimento gengival induzido pela fenitoína é uma complicação comum do uso contínuo da medicação. Este artigo apresenta um caso de crescimento gengival excessivo que dificultava a função oral e comprometia a higiene oral e a estética, o qual foi tratado com uma combinação de terapias periodontais não-cirúrgicas e cirúrgicas. Paciente masculino de 39 anos de idade foi encaminhado para tratamento odontológico com várias queixas, especialmente do crescimento gengival superior e

inferior que prejudicava a fala e deglutição. Profundidades de sondagens severas generalizadas e perda óssea foram detectadas. Diagnóstico de crescimento gengival induzido pela fenitoína e periodontite crônica foi estabelecido. O plano de tratamento consistiu de terapia conservadora com educação, motivação e meticulosa instrução de higiene oral em associação com raspagem e alisamento corono-radicular. Durante o período de reavaliação, uma acentuada redução nos parâmetros clínicos foi observada, principalmente uma redução das profundidades de sondagem. Terapia cirúrgica para remoção do excesso de tecido gengival também foi realizada para conseguir redução das bolsas. Terapia periodontal de suporte foi proposta e o paciente está atualmente sob acompanhamento por um período de 4 anos. O manejo do crescimento gengival induzido pela fenitoína pode ser obtido pelo uso de procedimentos periodontais combinados com uma boa higiene oral e cuidados periodontais de suporte.

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Received March 21, 2014
Accepted November 24, 2014