SEVERE PHENYTOIN-INDUCED GINGIVAL ENLARGEMENT ASSOCIATED WITH PERIODONTITIS: RATIONAL MODEL FOR ITS CLINICAL MANAGEMENT

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ABSTRACT

This case report documented a severe gingival enlargement associated with periodontitis in a patient under antiepileptic therapy and provided a rational model for its clinical management. Initially, full-mouth scaling and root planing, oral hygiene instructions and phenytoin withdrawal were performed. However, clinical results demonstrated just partial resolution of upper jaw gingival hyperplasia after non-surgical therapy. Subsequently, surgical therapy was indicated for the upper jaw teeth. After the surgical therapy, complete reduction of gingival enlargement was observed. This report described the challenges faced by the oral and medical health practitioners in developing appropriate prevention and treatment for antiepileptic drug users, particularly for periodontal patients.

Key words: periodontitis, phenytoin, gingival hyperplasia, periodontal therapy
RESUMO

O presente relato documentou o aumento gengival induzido por fenitoína associado com periodontite apresentado por uma paciente sob terapia antiepiléptica, e propôs um modelo adequado para o manejo clínico do caso. Inicialmente, realizou-se raspagem e aplainamento radicular completos, instruções de higiene bucal e substituição da fenitoína. Mas os resultados clínicos demonstraram resolução incompleta da hiperplasia do arco superior após a terapia não cirúrgica. Por isso, subseqüentemente, foi indicada para o arco superior a terapia periodontal cirúrgica, que acarretou em resolução completa do aumento gengival. Este relato de caso descreveu as dificuldades encontradas por profissionais médicos e odontológicos para o desenvolvimento de métodos preventivos e terapêuticos adequados para usuários de drogas antiepilépticas, particularmente pacientes com doença periodontal.

Palavras-chave: periodontite, fenitoína, hiperplasia gengival, terapia periodontal

INTRODUCTION

Antiepileptic drugs are among the most commonly prescribed centrally active agents, widely used to treat conditions other than epilepsy, including migraine, neuropathic pain, anxiety and bipolar disorder. Although the mechanisms of action of the antiepileptic drugs are not completely understood it has been demonstrated that blockade of voltage-dependent sodium channels is a primary action of these compounds (PERUCCA, 2005). The tolerability profiles of available antiepileptic drugs differ substantially from one drug to another, and the likelihood of appearance of specific adverse effects represents the most important consideration in selecting the drug to be prescribed in a given patient. These adverse effects can be broadly classified into those that are reversible and dose dependent, such as ataxia, sedation, dizziness, cognitive dysfunction, and those that are chronic and not rapidly reversible, such as changes in body weight, hirsutism and gingival hyperplasia (PERUCCA, 2005).

Phenytoin is an antiepileptic drug commonly used as a therapeutic agent in patients with epilepsy, either alone or in combination with other anticonvulsant drugs (HALLMON; ROSSMANN, 2000; PERUCCA, 2005). Advantages of phenytoin include its effectiveness, low cost, availability and once daily administration. Among

the side-effects of phenytoin therapy, gingival hyperplasia is a well recognized adverse effect, occurring in an average of approximately 50% of patients receiving this drug (ANGELEPOULOS; GOAZ, 1972; HALLMON; ROSSMANN, 2000). Although several studies on phenytoin-induced enlargement have been conducted, the pathogenesis of this gingival lesion is still not understood. Associations have been suggested between phenytoin-induced gingival enlargement and multiple anti-epileptic therapies, plaque accumulation, host genetic predisposition and reduced serum folate levels (JOHNSON et al., 1990; HALLMON; ROSSMANN, 2000).

The higher prevalence of gingival overgrowth observed in patients undergoing anticonvulsant treatment has been related to phenytoin in association with other medicines, such as phenobarbital and carbamazepine. These associations may induce phenytoin metabolism in the liver, resulting in an increment in phenytoin metabolites (HASSELL; HEFTI, 1991; BRUNET, L. et al.; 2001). High levels of dental plaque and calculus have also been reported to be a critical cofactor for the development of phenytoin-induced gingival hyperplasia (HALLMON; ROSSMANN, 1999). It has been documented that risk factors associated with phenytoin-induced gingival enlargement may have a synergistic effect and that bacterial plaque seems to be the most important determinant of its severity (MAJOLA, M. P. et al., 2000). Additionally, the role of genetic factors in these gingival lesions has been investigated; it has been proposed that human gingiva contains genetically-predetermined phenytoin-sensitive subpopulations of fibroblasts and, for this reason, phenytoin reacts with some but not with all cells (HASSELL; GILBERT, 1983; HASSELL; HEFTI, 1999) stimulating greater collagen and protein production (JOHNSON et al., 1990). Finally, it is well established that phenytoin may interfere with folic acid absorption and metabolism, leading to a significant decline in folate levels. This phenomenon has been suggested to be one of the most important promoters of phenytoin-induced gingival hyperplasia (NORRIS; PRATT, 1975; MAJOLA et al., 2000).

We recently experienced a case of severe gingival enlargement associated with periodontitis in a patient under combined antiepileptic therapy (phenytoin/ carbamazepine). Therefore, this report describes the clinical history and management of a case of phenytoin-induced gingival hyperplasia associated with periodontal disease. Furthermore, this case report aimed to demonstrate the value of consultative planning between oral care practitioners and physicians, regarding the prevention and treatment of gingival lesions in these medically compromised patients.
CASE REPORT

A 33-year-old female was referred to the Periodontics Department of the Guarulhos University from her dentist, demonstrating areas of gingival hyperplasia affecting both maxilla and mandible for over 1 year. The patient had been taking phenytoin (Hydantal®, Aventis Pharma Ltda., Suzano, SP, Brazil) and carbamazepine (Tegretol®, Novartis Pharmaceuticals, São Paulo, SP, Brazil) over a period of 4 years, as recommended by her neurologist for seizure control.

The enlarged gingiva completely covered most of her anterior teeth and protruded from the mouth, resulting in an aesthetic disfigurement (Figure 1). The first clinical oral examination revealed a severe enlargement of the interdental papilla, extending to the facial and lingual gingival margin, resulting in the clinical presence of pseudoclefts. The vertical and horizontal overgrowth was generalized throughout the mouth, but was more severe in the right maxillary region. Coronal progression of the gingival overgrowth partially obscured the crowns of some teeth. This enlarged gingiva was characterized by soft, friable, painful and granular tissue, showing signs of inflammation such as swellings, and a bright red and shiny surface (Figure 2).

Figure 1 – This photograph illustrates the enlarged gingiva covering most of the anterior teeth and protruding from the mouth, resulting in an esthetic disfigurement

Figure 2 – Aspects of the soft, friable and granular tissue, showing signs of inflammation such as swellings, bright redness and suppuration

The patient’s oral hygiene was poor, accompanied by marked plaque and calculus accumulation around all the teeth. Although the patient claimed to brush her teeth daily, she was not achieving effective plaque removal because of the severity of the lesions. It was also observed that some teeth had been previously lost (17, 22, 27, 38, 37, 36, 47 and 46) and that the eruption of tooth 18 was delayed.

Bleeding and suppuration from the gingival pockets occurred spontaneously and easily on probing. Clinical measurements were plaque index (PI), bleeding on probing (BOP), suppuration (SU), pocket depth (PD), gingival recession (GR) and clinical attachment level (CAL). These measurements were made on 6 aspects per tooth (mesio-vestibular, mid-vestibular, disto-vestibular, mesio-lingual, mid-lingual, and disto-lingual), using a manual periodontal probe (Hu-Friedy Co, Chicago, IL). Bleeding on probing was assessed simultaneously with the probing measurement, and the presence or absence of bleeding up to 15 seconds after probing was recorded. The presence of plaque, bleeding and suppuration were noted for each dental surface and expressed as percentage of sites under evaluation. In addition, dental mobility (DM) and furcation involvement (FI) were also assessed.

BOP, PI and SU mean values were 100%, 100% and 86%, respectively. The periodontal clinical examination revealed that the deeper probing depths (≥ 10mm) and clinical attachment levels (≥ 7mm) were more common in buccal, lingual and approximal maxillary sites. No gingival recession was observed. Severe DM was also noted in teeth 11 and 21 and FI was present in teeth 16 and 26.

Periapical radiographies, taken at that time, showed generalized horizontal and vertical alveolar bone resorption, characterizing advanced periodontitis. This radiographic bone loss was more pronounced in the anterior and molar maxillary region.

The enlargement of the gingival tissue associated with periodontitis also resulted in malpositioning and emigration of anterior upper jaw teeth, interfering with the masticatory function and speech (Figure 3).
TREATMENT

An initial, single episode of crown and root debridement was performed under local anesthesia using manual mechanical scaling and root planing. This first treatment protocol also integrated oral hygiene instruction, including the Bass technique of brushing and interdental cleaning with dental floss and interdental brushes. Subsequently, the patient received isolated scaling and root planing of deep and/or bleeding sites throughout the entire four weeks following the initial debridement. Oral hygiene instruction reinforcement and tooth polishing with rubber cup and abrasive paste were provided in all subgingival instrumentation visits. 0.12% chlorhexidine gluconate rinses were also prescribed twice a day as an adjunctive antimicrobial. The periodontal reevaluation demonstrated that the initial periodontal treatment provided a beneficial effect, however, the gingival lesions did not completely resolve. At this moment, the patient’s oral hygiene was still poor, therefore, once again, oral hygienic reinstruction and professional plaque control were performed (Figure 4).

Figure 4 – This photo illustrates the beneficial effect of the initial periodontal treatment and the partial resolution of gingival enlargement. This photograph also illustrates the patient’s poor oral hygiene at that moment.

After this initial periodontal therapy, the neurologist was asked to change the ongoing anti-convulsant program, establishing a level of seizure management without sacrificing attentiveness and mood control. There was no reluctance of the physician to adjust the therapy and the patient started to take phenobarbitone (Gardenal®, Rhodia Farma, São Paulo, SP, Brazil) and carbamazepine. Additional periodontal treatment was performed for the upper jaw after the patient’s oral hygiene improvement, consisting of surgical procedures for the removal of residual calculus and hypertrophic soft tissue. One incisinal biopsy from the anterior enlarged gingival was harvested for histopathological evaluation and the final diagnosis was reported as inflammatory fibrous hyperplasia (Figure 5).
The patient showed an overall healing response to these medical and periodontal treatments, resulting in total remission of the gingo-val lesions. At this time, BOP, PI and SU mean values were 15%, 30% and 0%, respectively.

Subsequently, the patient was engaged in a monthly regular periodontal maintenance program and periodontal stabilities were reached after 6 months (Figure 6). The malpositioning and emigration of teeth were partially restored (Figure 7). A provisory removable partial denture for the lower jaw was made in order to fulfill the functional needs of the patient and she was referred for operative dentistry, orthodontic and definitive prosthetic treatments.

DISCUSSION
Gingival enlargement has been described in individuals using phenytoin dating back to 1939 (ANGELOPOULOS; GOAZ, 1972; ANGELOPOULOS, 1975). Significant correlations have been also
demonstrated between the occurrence and severity of this phenytoin-induced gingival enlargement and the presence of plaque and calculus accumulation (HASSSELL et al. 1984; PENARROCHA-DIAGO; BAGAN-SEBASTIAN; VERA-SEMPERE, 1990). In this article, we presented the clinical features of a severe phenytoin-induced gingival enlargement associated with periodontitis and showed a combined treatment approach, including periodontal therapy and medication adjustments. This report aimed to highlight that the ideal model for prevention and management of phenytoin-induced gingival hyperplasia should be discussed within the context of consultative planning between oral care practitioners and physicians.

Firstly, the physician should be aware of the prevalence and risk of gingival overgrowth induced by phenytoin and other antiepileptic drugs in order to refer patients to preventive periodontal practices and early diagnosis of this condition. In this case, the appearance of the initial lesions indicated to us that the gingival side-effects could be minimized with a preventive dental program before the beginning of the antiepileptic therapy. Some studies have already demonstrated the benefits of a preventive periodontal program for outpatients taking phenytoin for seizure control, including a dental prophylaxis and reinforcement of oral hygiene at frequent intervals (NAVARRO; CORRELL, 1976; PIHLSTROM et al., 1980 17). Although the preventive program is not able to completely prevent the occurrence of gingival enlargement, this overgrowth could be minimal or imperceptible to many of the subjects (PIHLSTROM et al., 1980). Therefore, in contrast to our patient, individuals may begin a preventive dental program as soon as they begin taking phenytoin, especially with the presence of periodontal attachment loss.

In addition, in antiepileptic patients, periodontal therapy could be planned in conjunction with medication alternatives and adjustments. It is important to emphasize that the patient should never
be made to suffer more from the side effects of an epilepsy treat-
ment than from the consequences of the disease (PERUCCA, 2005).
In the current case report, the lesions were responsible for serious 
psychosocial problems such as discomfort, malodor and esthetic 
disturbance. In this context, an attempt should be made to tailor the 
expected side-effect profile of the antiepileptic drug to the charac-
teristic of the individual. Medicines causing gingival enlargement,
for example, may not be a good choice for periodontal and poor oral 
hygiene patients.

In recent years, the number of commercially available antiepilep-
tic drugs has increased steadily (PERUCCA, 2005). In phenytoin-
administered patients, consultations with the physician should also 
include phenytoin withdrawal and its replacement for therapeutic 
alternatives. The logical approach for the control of gingival enlarge-
ment, induced by antiepileptic drugs, should be the reduction of 
the dose of the drug or its suppression and substitution for another 
(SEYMOUR; SMITH; TURNBULL, 1985; DAHLLÖF; AXIO; 
MÖDEER, 1991). In this case, her neurologist prescribed pheno-
obarbitone/carbamazepine as a substitute for phenytoin/carbamaze-
pine and she has been taking this alternative therapy for at least 
the last 6 months. Phenobarbital remains a commonly prescribed 
alternative antiepileptic medication that presents some association 
with gingival overgrowth, but the occurrence of this side effect 
is considered infrequent compared with phenytoin (HALLMON; 
ROSSMANN, 1999). Similarly, carbamazepine has not been asso-
ciated with gingival enlargement and is considered a useful alter-
native medication in the treatment of patients with seizures that are 
at risk of gingival overgrowth.

It has been documented that phenytoin-induced gingival hyperpla-
sia is reversible following cessation of drug use (NORRIS; PRATT, 
1974; DAHLLÖF; AXIO; MÖDEER, 1991). Likewise, several stu-
dies have demonstrated the relationship between dental plaque and 
phenytoin-induced gingival enlargement (JOHNSON et al., 1990), 
demonstrating the efficacy of scaling, root planing and anti-plaque 
agents in the resolution of this side-effect (PIHLSTROM, 1990). Ho-
wever, in the current case report, although phenytoin withdrawal and 
scaling and root planning effectively reduced gingival hyperplasia 
and inflammation, surgical treatment was required for upper jaw to 
eliminate residual gingival overgrowth and calculus. The remaining 
excessive tissue and calculus were removed using a conventional 
flap, after the physician’s determination of the patient’s risk status 
relative to proposed surgical procedures. After surgery, healing was 
uneventful and significant regression of the initial condition (gin-
gival suppuration, bleeding on probing and gingival hyperplasia as well as periodontal pocket) was observed, permitting additional dental care such as dentistry, prosthetic and orthodontic. As described previously, the patient had severe psychological problems related to her esthetic appearance. Despite gingival recessions, the psychological benefits of the cosmetic improvement by such treatments must not be underestimated.

Finally, we initiated our patient on a maintenance and follow-up program in order to prevent the reoccurrence of periodontitis and hyperplasia. The maintenance program consists of a medical history update, reevaluation of clinical periodontal parameters, prophylaxis and reinstruction of oral hygiene. Based on scientific evidence, a supportive periodontal therapy should be introduced after hyperplasia reduction for all epileptic patients (PIHLSTROM, 1990).

The findings of the present report provide important evidence of the complexity of a phenytoin-induced gingival enlargement associated with a case of periodontitis and reinforces the hypothesis that periodontal therapy should be realized in conjunction with physician managements. Ideally, the antiepileptic administrated patients should look forward to a multidisciplinary treatment care and more rational antiepileptic therapies.

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