Successful management of phenytoin and phenobarbitone induced gingival enlargement: A multimodal approach

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Abstract

Medication-related gingival enlargement is a common reactionary phenomenon that occurs with the use of several types of therapeutic agents, including antiepileptic drugs (AEDs). This disorder has been documented since 1939, shortly after the introduction of phenytoin. In the present case, a concise review of literature concerning the etiopathogenesis and management of AEDs (phenobarbitone and phenytoin) induced gingival enlargement has been described. It is vital that not only the periodontist, but also dental surgeons and medical practitioners should become aware of the potential etiologic agents, characteristic features, and the differential diagnosis of drug induced gingival enlargement in order to be able to prevent, diagnose and successfully manage the condition.

Keywords: Gingival enlargement, metronidazole, phenobarbitone, phenytoin, platelet rich fibrin

Introduction

Gingival enlargement produces adverse esthetic challenges, functional impairment and clinical symptoms which includes gingival pain, tenderness, bleeding, speech disturbances, abnormal tooth movement and dental malocclusion. It also increases the risk for the development of caries and periodontal disorders. This condition is ascertained to be caused by medications like antiepileptic drugs (AEDs), calcium channel blockers and immunosuppressants, genetic abnormalities, such as hereditary gingival fibromatosis, proliferative lesions, etc.[1]

Epilepsies are a group of disorders characterized by paroxysmal cerebral dysrhythmia, manifesting as brief periods of loss or disturbance of consciousness. It was correctly recognized as the "disease of lightening" by JH Jackson a century ago and is the most common chronic neurological disorder in human.[2]

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A number of AEDs have been used successfully to treat this disease but like any other drugs these antiepileptic medications have various side effects, one of which is gingival enlargement. Drug-induced gingival enlargement was first observed in patients who were taking phenytoin for epilepsy, with approximately 50% of incidence.[3] Three significant factors which are important in the expression of these gingival changes comprises: drug variables, plaque-induced inflammatory changes in the gingival tissues and genetic factors-the latter determining the heterogeneity of the gingival fibroblasts.[4]

This article focuses on a case of more commonly used AED phenytoin and rarely used phenobarbitone induced gingival enlargement which was successfully managed with appropriate periodontal therapy and platelet rich fibrin (PRF), a biological bandage.

Case Report

A 35-year-old male patient came to the Department of Periodontics with the chief complaint of difficulty in speech, mastication, pain and bleeding, while brushing due to swollen gums. The medical history revealed that the patient was epileptic and was under a combination of AEDs which encompassed phenytoin, carbamazepine and eslicarbazepine for 8 years and phenobarbitone for the last 6 months. The family history was not significant. The history of present illness demonstrated that the patient noticed the enlargement for the past 6 months which was painless and progressive in nature.

On intraoral clinical examination, there was generalized gingival enlargement with few areas covering the occlusal aspect of the posterior teeth [Figure 1]. The enlargement was pale pink in color, firm, resilient with minutely lobulated

surface except in areas superimposed with inflammation. Due to the enlargement, patient showed difficulty in speech, mastication and maintenance of oral hygiene. Orthopantomogram showed uniform horizontal bone loss [Figure 2]. Routine blood investigations failed to show any abnormality. Hence, a diagnosis of AED induced gingival enlargement was arrived. The treatment plan was put forward which started with the extraction of hopeless teeth (#11 and #25) followed by phase I therapy to reduce the inflammation and phase II gingivectomy procedure to reduce the bulk tissue.

Prior to the surgery, the patient underwent extraction of #11 and #25. This was followed by phase I therapy along with topical application of 10% metronidazole gel. The patient was advised to take folic acid supplements (1 mg 1-3 times a day) as phenytoin decreases folate absorption and increases its excretion. Once the inflammation was reduced the patient was taken for surgery.

After obtaining the physician's consultation regarding patient's medical condition for the surgical procedure, the procedure was explained to the patient and an informed consent was obtained. The gingivectomy procedure was planned for one quadrant every appointment at an interval of 1 week. After achieving adequate anesthesia using 2% xylocaine HCl with adrenaline (1:2,00,000), precise identification of the pockets on all the surfaces of all teeth within the surgical field was done with the help of a pocket marker at three points/tooth (mid radicular, mesial and distal line angles) on the facial/buccal and lingual/palatal aspects. An external bevel incision was given using no 15 Bard Parker blade and Kirkland surgical periodontal knife [Figure 3]. Interdental incisions were made using Orbans knife and the bulk of tissue was removed with the help of curettes. Tissue tags were removed with Goldman fox surgical scissors. The surgical site was then inspected for any residual debris. PRF was placed [Figure 4] and protected with a tin foil in areas where bone exposure was encountered over which periodontal dressing was placed. The patient was given post-operative instructions and was instructed to take analgesics (combination of paracetamol-500 mg and diclofenac-50 mg) thrice daily for 3 days. The same surgical procedure was carried out for the rest of the quadrants. Healing was uneventful. Patient was kept under regular follow-up and oral hygiene instructions were reinforced at every appointment.

The excised specimen was sent for histopathology report. The biopsy specimen showed similar features given in literature.[1] Specimen showed dense fibrous connective tissue consisting of numerous collagen bundles with moderate to severe chronic inflammatory cell infiltrate predominantly consisting of lymphocytes and plasma cells. The epithelium was nonkeratinized in some areas and parakeratinized in other areas with long thin rete ridges in few areas and blunt short rete ridges in the rest of the areas [Figure 5].

Discussion

The American Academy of Periodontology 2001 defines drug-induced gingival enlargement as an overgrowth or increase in size of gingiva resulting in whole or part from systemic drug use.[5] Currently, there are over 20 medications from three pharmaceutical categories including anticonvulsants, calcium channel blockers and immunosuppressants that are associated with gingival enlargement.[6] Gingival enlargement is one of the most frequent adverse effects associated with the administration of phenytoin. Incidence rates have ranged from 3%-93%, but about 50% of patients on long-term phenytoin therapy develop gingival enlargement.[1] Phenobarbitone induced gingival enlargement is poorly documented and its prevalence is <5%.[7] In our case, the patient was under phenytoin medication for 8 years and phenobarbitone for the past 6 months. Patient was also under carbamazepine and eslicarbazepine medications making the condition more complex. However, these drugs are very uncommon in producing gingival enlargement. The exact mechanism of drug-induced gingival enlargement remains an enigma. There are several proposed hypotheses, some of which are controversial; however, the cause is likely multifactorial.[8-12] It was proposed that phenobarbitone induced gingival enlargement results in the formation of pseudoepitheliomatous hyperplasia due to alteration in the epidermal growth factor/transforming growth factor (TGF)-α ratio.[12]

There is an inconclusive relationship between the severity of the gingival enlargement and drug dosage, duration of therapy and drug concentrations in serum, saliva and gingival crevicular fluid.[4,7] It has been found out that the incidence and severity of phenytoin induced overgrowth is greatest on the labial surfaces of maxillary and mandibular anterior teeth whereas for phenobarbitone, severity is more in the posterior regions compared with anterior regions.[13] In the present case, there was severe gingival enlargement in the maxillary posterior and mandibular anterior region when compared to maxillary anterior and mandibular posteriors respectively which was unique for this case. Moreover, enlargement was more on the left side when compared to right.

One of the foundations for treatment of all drug-induced gingival overgrowths is discontinuation of the medication along with drug substitution. However, in the present case, it was not possible as those drugs were lifesaving drugs for the patient according to the patient's physician. Hence we proceeded with the best possible treatment in order to enable the patient to maintain his oral hygiene.

Given the significance of plaque and calculus as risk factors for exacerbation of gingival overgrowth, initial periodontal therapy was aimed at non-surgical periodontal treatment which included scaling and root planing, usage of 0.12% chlorhexidine mouthwash and regular application of metronidazole gel. In our case, patient was asked to use metronidazole gel as various studies[14-16] have evidenced

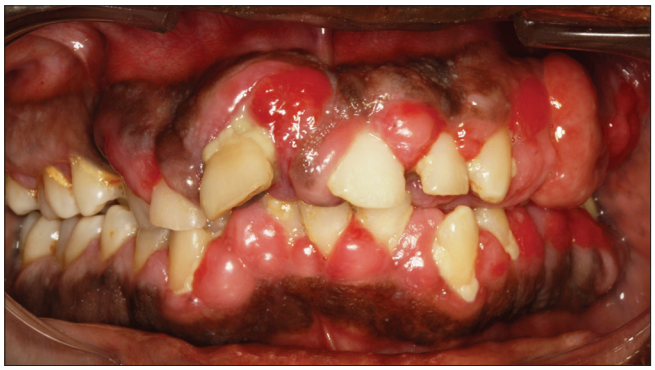

Figure 1: Pre-operative view

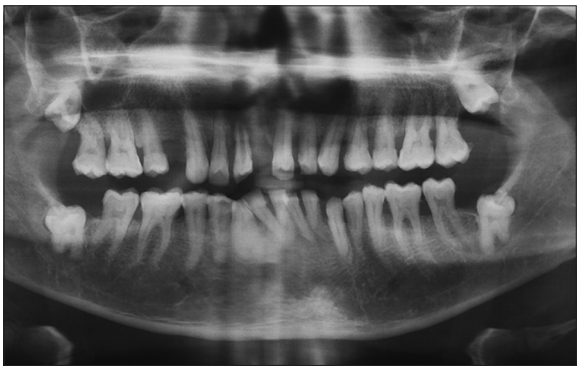

Figure 2: Orthopantomogram

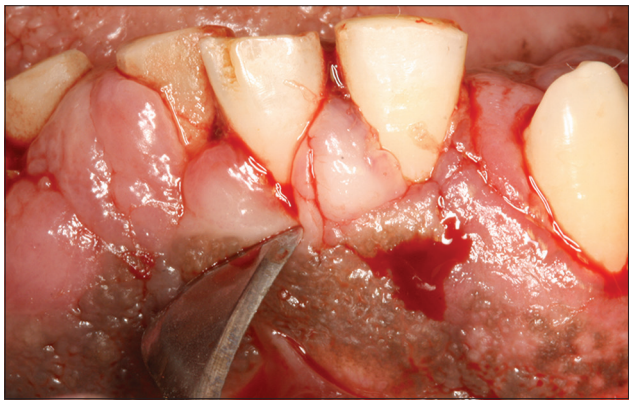

Figure 3: Kirkland knife for gingivectomy

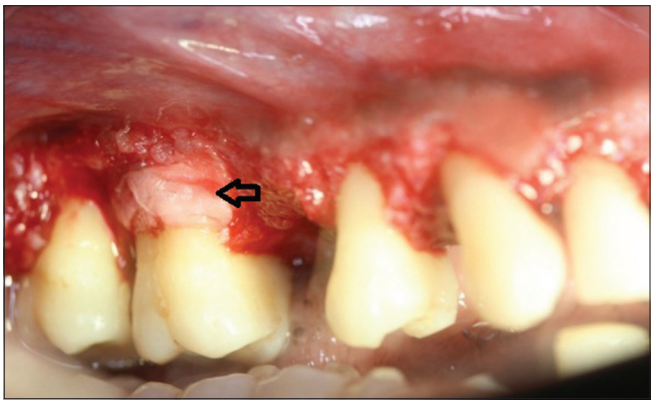

Figure 4: Placement of platelet rich fibrin

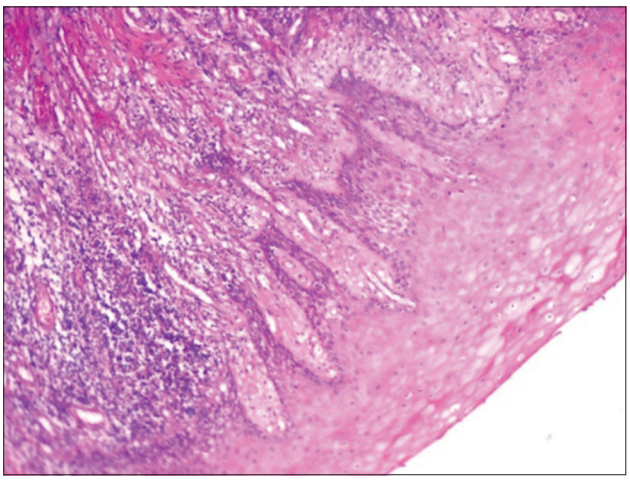

Figure 5: Photomicrograph (×40)

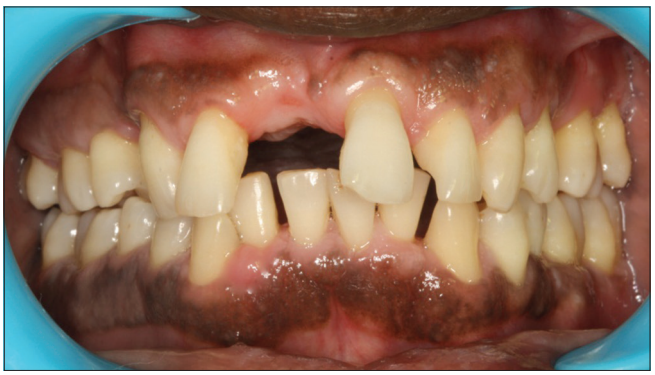

Figure 6: 12-months postoperative view

its effectiveness in treating gingivitis. Patient was also instructed to take folic acid on regular basis for 30 days as numerous literatures have shown that phenytoin may precipitate folic acid deficiency and megaloblastic anemia.[3,17]

Unfortunately, these measures failed to resolve the overgrowth to a satisfactory level, as the gingival lesions have been long-standing. Hence, surgical intervention was taken into consideration. Simple gingivectomy procedure along with adequate plaque control was opted over periodontal flap surgery due to generalized moderate bone loss and adequate width of keratinized gingiva.[18]

Reconstruction of exposed raw wound surfaces after gingivectomy procedures allegedly considered challenging earlier is now overcome in the modern era of tissue engineering by using PRF, an autologous blood borne growth factor. In the present case, gingivectomy led to the bone exposure especially in posterior areas. Futhermore, the presence of denuded bone has been related to increased incidence of infection which can further complicate the wound.[19] Hence, to fasten the wound healing process we

decided to use autologous PRF to shield the open wound which acts as a matrix for neoangiogenesis and epithelial cell migration.[20-23] PRF also consists cytokines such as interleukin 1 beta (IL-1ß) -4, and -6, and growth factors such as TGF-ß1, platelet derived growth factor (PDGF), vascular endothelial growth factor[23] and connective tissue growth factor.[19,21] Thus, PRF has been substantiated in protecting open wounds and accelerating the healing process.[19]

Relapse may occur 3-6 months after surgical treatment,[3] but in the present case 12 months recall visits showed no recurrence of the enlargement [Figure 6]. While, it may be prevented through scrupulous periodontal maintenance and home care, it is essential for the periodontist to work together with the patient's physician in order to productively treat this condition once it occurs. One of the main goals of the clinician is to satisfy the patient's needs. In the present case, the patient was satisfied with the treatment as all his grievances like difficulty in speech, mastication, pain, and bleeding while brushing due to swollen gums were resolved.

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