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Case Report Dental Science

Drug induced Gingival Enlargement (Phenytoin): a case report

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ABSTRACT Gingival overgrowth (GO) is a side effect associated with some distinct classes of drugs, such as anticonvulsants, immunosuppressant, and calcium channel blockers. GO is characterized by the accumulation of extracellular matrix in gingival connective tissues, particularly collagenous components, with varying degrees of inflammation. One of the main drugs associated with GO is the antiepileptic phenytoin, which affects gingival tissues by altering extracellular matrix metabolism. Nevertheless, the pathogenesis of such drug-induced GO remains fulfilled by some contradictory findings. This paper aims to present the most relevant studies regarding the molecular, immune, and inflammatory aspects of phenytoin-induced gingival overgrowth.

KEYWORDS : Gingival enlargement, Phenytoin.

INTRODUCTION :

The term hyperplasia used by some is inappropriate because enlargement does not result from an increase in number of cells but rather an increase in volume of extracellular matrix of gingival connective tissue. There are different views in the literature if this is hyperplasia of the gingival epithelium or sub-mucosal connective tissue or exaggeration of normal process of cell proliferation and differentiationAn increase in size of gingiva is called as gingival enlargement / overgrowth.[1] It was first reported with the use of Phenytoin in 1938.[2] The growth starts as painless, beadlike enlargement and may extend to involve a considerable portion of the crown. It can adversely affect speech, mastication, tooth-eruption and esthetics. It is clinically an apparent enlargement of the papillary and marginal gingivae.

Gingival swelling is almost universally the result of the fluid accumulation within the tissues: edema. Affected gingival tissues are soft in consistency, generally more or less erythematous, and bleed without exception when gently probed.

Edematous swelling of gingiva is completely reversible in the individuals (healthy), if the local causative agent, microbial plaque is regularly and effectively removed by mechanical teeth-cleaning procedures.

This paper describes a case of Drug –induced gingival enlargement (Phenytoin).

CASE DESCRIPTION :

A 20- year old patient came to the OPD in the Department of periodontics, Daswani Dental College and research centre (DDCRC), Kota (Raj.) with the chief complaint of gingival overgrowth in entire mouth. She noticed it before 2-months. She was suffering from epilepsy from past 2 years so her physician prescribed the phenytoin drug due to which there was generalized gingival over-growth (Fig:1). The patient was unable to maintain her oral hygiene so she came to the department for the treatment.

Clinical Findings:

The patient came to the department complaining about the enlargement which was initially involving the lower anteriors (Fig: 2). Gradually she noticed enlargement covering the whole mouth. She noticed it within 6 months. The growth was not associated with pain but patient was having problem in chewing food. The resultant enlargement was the combination of the increase in size caused by the drug and the complicating inflammation was caused by bacteria. (Fig: 3) It showing the Pre-operative OPG of the case which is showing the pseudo pockets. (Fig: 4) Showing the patient undergoing surgery. (Fig: 5) The picture showing after the treatment of surgery healing phase.

Histopathology:

The biopsy was performed and the given soft tissue section reveals fibrocellular connective tissue with numerous collagen fibres containing firbroblasts, enlarged blood vessels and extravasted RBCs are seen in abundance. The overlying epithelium is para-keratinized stratified squamous in nature (Fig: 6).

Treatment:

After clinical examination, Phase I therapy was initiated and the drug phenytoin was substituted with the valproic acid (sodium valproate). Surgical therapy (Gingivectomy) was done in all the quadrants after evaluation of Phase I. The surgical therapy was performed in different sittings and the patient was recalled for the follow-up so that the patient's oral hygiene was maintainedproperly.

Postoperative care :

The surgical wounds were covered with a non-eugenol periodontal pack (Coe-Pak, GC America, Inc.). The following postoperative instructions were given: for the first 24 hours, only liquids, semisolids or finely minced foods are recommended, avoid hot foods and/or liquids, and apply ice intermittently on the face over the operated area. Chew on the un-operated side of the mouth.

Do not brush over the periodontal pack. Use chlorhexidine oral rinse (as prescribed) no less than 24 hours after surgery, and do not rinse vigorously on the first day.Contact the clinician if the periodontal pack fractures, or if uncontrollable postoperative bleeding and/or unbearable pain occurs.The patient was prescribed an antibiotic

(amoxicillin 500 mg TID for 3 days). For management of postoperative pain, thepatient was also prescribed anti-inflammatory analgesic drugs (Ibuprofen 400 mg and Paracetamol 325 mg TID after meals for 3 days). In case of hyperacidity, anantacid (pantoprazole 40 mg before meals BID for 3 days) could be consumed. After 1 week, the sutures and periodontal pack were removed, and the surgical wound was examined. The patient was recalled 1 month and 3 months postoperatively to observe the healing progress

Prevention :

In the susceptible patient, drug-associated gingival enlargement may be ameliorated, but not prevented, by elimination of local irritants, meticulous plaque control, and regular periodontal maintenance therapy. A 3-month interval for periodontal maintenance therapy has been recommended for patients taking drugs associated with gingival enlargement. Each recall appointment should include detailed oral hygiene instructions and complete periodontal prophylaxis, with supra- and subgingival calculus removal as needed. Topically applied 0.12% chlorhexidine can reduce the severity of gingival enlargement, and thus may be a valuable tool inthe prevention and overall management of gingival enlargement in humans.

DISCUSSION :

Pathogenesis of PGO

The mechanisms that trigger drug-induced gingival enlargement, have not been completely understood. Some studies suggest that phenytoin inhibits the production of extracellular matrix by gingival fibroblast and cell proliferation [3, 4]. In contrast, others showed that the accumulation of proteins in extracellular matrix, particularly collagen, may occur due to an imbalance between the synthesis and the degradation of extracellular matrix as the possible cause of the overgrowth [5]. Also, there is some evidence of decreased collagen production after phenytoin administration in vitro [6]. Kato et al. [7] showed a reduction in mRNA expression of collagen type I and III associated with a higher density of these fibers ingingival overgrowth. These results suggest that the imbalance that leads to gingival overgrowth might be related to decreased collagen degradation, not to an increase on its synthesis.

Several mechanisms are involved in the development of gingival overgrowth.

- Phenytoin induces a decrease in the Ca2+ cell influx leading to a reduction in the uptake of folic acid, thus limiting the production of active collagenase. Inoue and Harrison [8] suggested that patients taking phenytoin and a supplement of folic acid had reduced or no gingival enlargement. Studies have also showed that patients receiving folate had lower recurrence of gingival enlargement after its surgical removal [9, 10, 11] In opposition to these data, Majola et al. [12] found that serum folate levels did not have any significant association with PGO.

- Phenytoin also significantly decreases collagen endocytosis, which is related to a lower expression of α2β1-integrin [7]. Alpha-2-Beta-1-integrin functions as a specific receptor for collagen type I in fibroblasts and acts in the initial step of collagen phagocytosis, providing an adhesive interaction between fibroblasts and collagen [13]. Besides integrins, the receptor uPARAP/ENDO180 has also been described as one of the main receptors responsible for collagen phagocytosis[14].

- Other matrix metalloproteinases (MMPs) than collagenase are also responsible for the digestion of collagen fibers [15]. The enzymatic activities of MMPs are controlled by a tissue inhibitor (TIMP) whose function is to antagonize the actions of MMPs [7].

- Other important elements directly responsible for phenytoin-induced gingival overgrowth are cytokines. Phenytoin-activated fibroblasts produce large amounts of IL-6, IL-1, and IL-8. Such mediators are capable of activating the proliferation of T cells and the recruitment of neutrophils to the involved tissues, establishing a direct interaction between the immune system and the connective tissue. This interaction seems to be highly associated with fibrotic diseases.

- Evidence also points toward a role of dental plaque in the etiology of PGO through induction of a local inflammatory response, which is essential for the gingival overgrowth. A possible involvement of some bacterial species in the gingival lesion development havebeen studied. Takada et al. [16] found that Prevotella intermedia (Pi) prevalence is higher in patients with phenytoin induced gingival overgrowth than in patients taking the medication but who did not develop any enlargement, and also those who did not use phenytoin. Akiyama et al. [17] also found two bacterial species significantly associated with phenytoin induced gingival overgrowth, Treponema denticola (Td) and Porphyromonas gingivalis (Pg). Miyazaki also found increased levels of Td and Pg in severely affected PGO sites [18]. These findings are in contrast to the studies of Yamada et al. [19] and Smith et al. [20] who did not find differences in the oral microbial population of patients with and without PGO. In addition to bacteria itself the host response to these antigens also may be related to PGO. The bacterial components in dental plaque can be recognized by host cell Toll-like receptors (TLRs), which are sensors of pathogen-associated molecular patterns [21]. In this regard, phenytoin demonstrated some modulating effects over the TLRs.

- Growth factors such as CTGF, PDGF, FGF and TGF-β are found in higher levels in fibrotic tissues and play a role in PGO. Phenytoin may affect the production of IL-13 by an activation of Th2 cells, as well as it may induce the release of TGF-β, CTGF and other growth factors by macrophages, which leads, synergistically, to fibroblast proliferation, collagen biosynthesis, activation of TIMPs, inhibition of MMPs and ECM synthesis, characteristic processes observed in fibrotic lesions. In 2005, Kato et al. [7] showed that the gene expression of MMP-1, 2, and 3 was reduced by phenytoin administration, while the TIMP-1 mRNA was markedly augmented. This reduction of MMPs is believed to influence the PGO development

- The possible role of phenytoin on fibroblasts growth and death has also been investigated [22]. During healing, the transition from a granulation tissue to a remodeling tissue requires the apoptosis of fibroblasts. In wounds with inadequate apoptosis the formation of fibrotic tissues may occur. Thus, modulation of apoptosis could contribute to fibrosis in gingival tissues. The study of Kantarci et al. [22] demonstrated that fibroblast apoptosis is decreased in GO, and that this decrease may contribute to fibrosis, particularly in PGO. Thus, increased number of fibroblasts and ECM accumulation appears to be due, in part, to diminished fibroblast death in these tissues [23].

Treatment:

Our case was treated first with a non-surgical approach, including professional oral prophylaxis, prescription of chlorhexidine mouthwash, motivation of the patient for maintenance of oral hygiene with a soft toothbrush at home, and substitution of the offending drug. The sites which did not show improvement by the non-surgical approach were treated by surgical approaches.

Oral Prophylaxis:

Some studies have found significant correlationsbetween the incidence and/or severity of gingival overgrowth andthe amount of accumulated dental plaque and calculus [24,25]. Hassell & Page, 1978 [26] hypothesized that in non-inflamed gingiva, fibroblasts are less active or even quiescent, and do not respond to circulating

phenytoin, whereas fibroblasts within inflamed tissue are in an active state as a result of the inflammatory mediators and the endogenous growth factors present.

Ciancio et al 1972,[27] believed that inflammation is a prerequisite for development of the enlargement, which therefore could be prevented by plaque removal and fastidious oral hygiene.

In most of the enlargement cases, there are two components. Firstly, the fibrotic part due to drug-induced enlargement and secondly, the inflammatory edematous part. Edematous component of the enlargement of gingiva is completely reversible in the individuals (healthy), if the local causative agent, microbial plaque is regularly and effectively removed by mechanical teeth-cleaning procedures (reference). Other studies have shown that satisfactory oral hygieneis able to reduce the overgrowth, but not to completely prevent it [28, 29]. Thus, professional debridement with scaling and root planning has been shown to offer some relief in gingival overgrowth patients.

Drug Sustitution:

The most effective treatment of drug- related gingival enlargement is substitution of medication. Substitution of the drug should be done in conjunction with the patient's physician. So, the patient was referred to her physician who changed the drug to valproic acid.

Valproic acid has two opposing effects on phenytoin disposition: Displacing phenytoin from plasma protein binding sites, thereby enhancing the systemicclearance of total drug, andInhibiting phenytoin metabolism, thereby increasing the concentration of free drug in the serum.

Other than valproic acid, other possible drug substitutions for phenytoin are Lomatrigine, Gabapentin, Sulthiame, Topiramate, Carbamazepine.

Surgery

Gingival enlargement may persist even after drug substitution, oral prophylaxis and good plaque control. These cases need to be treated by periodontal surgery,either by gingivectomy or a periodontal flap. Incases of gingival over-growth,where true pockets are present flap surgeries are done after drug sustitution and if pockets are absent gingivectomy is performed. In this case there were no pockets so gingivectomy was performed.

Maintenance:

Recurrence of drug-induced gingival enlargement is a reality in surgically treated cases. Meticulous home care, chlorhexidine gluconate rinses, and professional cleaning can decrease the rate and degree at which recurrence occurs. A hard, natural rubber, fitted bite guard worn at night may also assist in the control of recurrence. Recurrence may occur as early as 3-6 months after the surgical treatment, but in general, surgical results are maintained for at least 12 months.

CONCLUSION:

GO is the most common in the young adults and children receiving phenytoin as antiepileptic therapy. Though poor oral hygiene and dental plaque are considered important risk factors in pathogenesis of GO, meticulous oral hygiene can minimize but not prevent the occurrence of GO. Considering alternatives to phenytoin or discontinuing it if feasible can definitely arrest or lessen the severity. Surgical correction remains the resort for those who have not responded well to these modalities. A lot more facets regarding pathogenesis remained to be discovered. Newer molecular approaches are needed to clearly establish the pathogenesis of GO and thereby providing novel information for future preventative and effective therapeutic modalities.

ATTACHMENTS

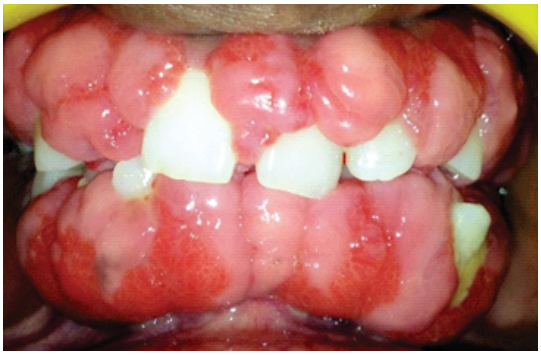

Figure 1: Pre-operative picture showing generalized gingival over-growth

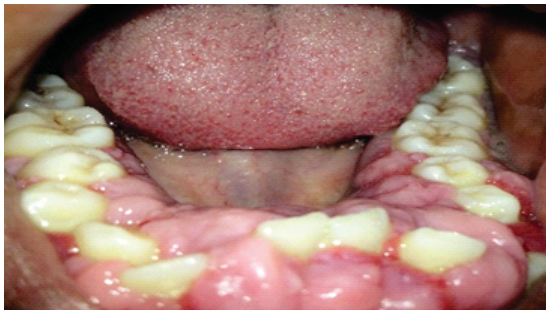

Figure 2: Pre-operative picture showing massive tissue fold covering considerable portions of the crowns

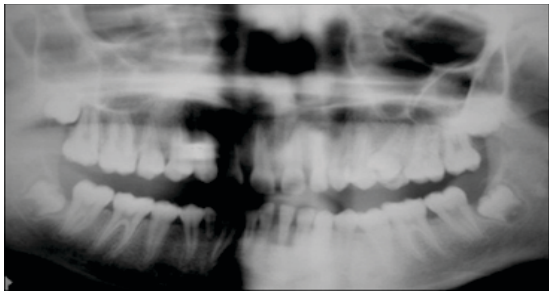

Figure 3: Pre-operative OPG showing pseudo pockets.

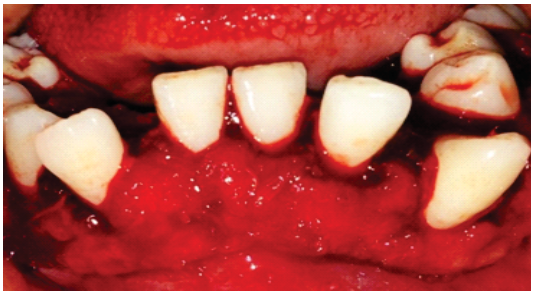

Figure 4: Intraoperative view during gingivoplasty

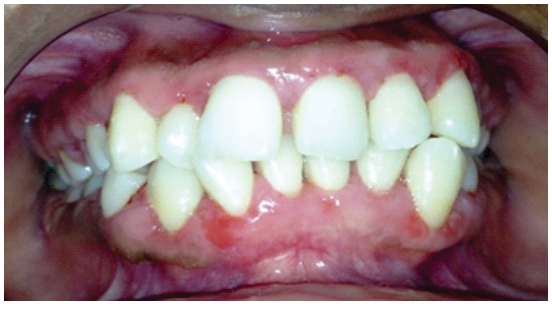

Figure 5: Post operative picture showing healing phase.

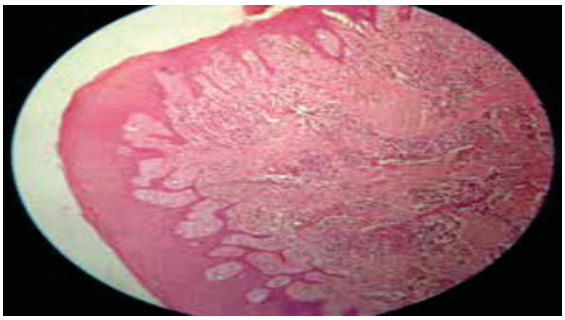

Figure: 6 histopathology section shows fibrocellular connective tissue with numerous collagen fibres containing firbroblasts, enlarged blood vessels and extravasted RBCs

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