"Phenytoin induced gingival enlargement": A dental awakening for patients with epilepsy

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Abstract
Epilepsy is a common chronic neurological disorder involving recurring seizures. It often has a bimodal age distribution, being more common during infancy and old age. Phenytoin remains to be the preferred drug in treating epilepsy, despite great progress in the field of understanding the etio-pathogenesis of epilepsy. Long-term use of phenytoin is associated with harmful effects, such as gingival enlargement, which is most often reported. This case reports the successful treatment of a young patient with phenytoin-induced gingival enlargement.

Keywords: Drug-Induced, Epilepsy, Gingival Enlargement, Phenytoin.

Introduction
Phenytoin induced gingival enlargement is seen in almost 50-100% of patients. 'Drug-induced gingival enlargement' (DIGE) refers to gingival hypertrophy or hyperplasia caused due to long term use of a drug such as phenytoin (PHT). Antihypertensive calcium channel blockers (Nifedipine, Verapamil, Diltiazem) and immune suppressants cyclosporine (Cyclosporin A) also induce the condition.(1)

Epilepsy is a chronic neurological disorder distinguished by repeated seizures and accompanied by sensory, autonomic or motor phenomenon with possible loss of consciousness.(2) The rate of epilepsy in India at about 5.59 per 1,000 populations according to recently meta-analyzed unpublished and published studies.(3) PHT (5,5 diphenylhydantoin) was first introduced as an antiepileptic drug by Merritt & Putnam in 1938.(4) Reports that linked gingival enlargement to PHT appeared within a year of the drug's initial use.(5) The aim of this report is to present a case of PIGO in a patient who was treated with alternative drug and change in dosage, and surgical periodontal therapies.

Case Report
A 21-year-old male with the main complaint of generalized swollen gums was referred to the Department of Periodontology, Subharti Dental College, Meerut. The patient hesitated to meet people due to the unaesthetic appearance and presence of oral malodor [Fig1].

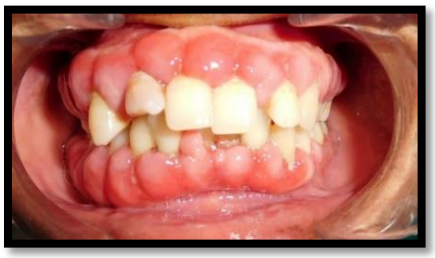

Fig1: Preoperative view

The patient's medical history showed that he had had epilepsy since he was 12 years old. He had not received many benefits from the various treatments he had tried, and had not had dental therapy in the past. The patient was using Eptoin 200 mg BD for the past 8 months.

The drug was associated with gradual gingival enlargement. Clinical examination showed the gingival tissues to be enlarged and bead-shaped, pale pink, fibrotic, and firm [Fig. 2 & 3]. Generalized bleeding on probing was present. Oral hygiene was poor.

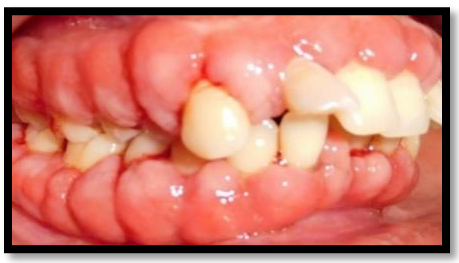

Fig 2: Right side pre-operative view

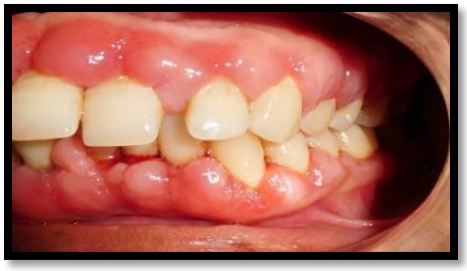

Fig 3: Left side preoperative view

Complete hemogram, CBC values were within normal limits. A generalized DIGE diagnosis was made. Complete oral prophylaxis was performed after consent from the patient and his physician. The patient was prescribed 0.2% Chlorhexidine mouthwash (10 ml BD for 21 days). The patient's condition improved after one week, and he was asked to use a soft toothbrush and warm saline gargles to maintain his oral hygiene.

Patient was advised to stop & change the Eptoin 200 mg drug to Levipil 500mg BD by his physician. Supportive periodontal therapy was performed after 1 month, 3 months, and 6 months. Surgical excision was prepared for after substantial enlargement of gingival tissues was observed at the 6-month visit. Written consent for the periodontal surgery was obtained from the patient after explaining the procedure.

The patient was given local anesthesia (2% lignocaine with 1:80,000 adrenaline) and a periodontal probe was used to explore the pockets on each surface and mark them with a pocket marker. Each pocket's course was outlined on each surface by marking it in several areas. A No. 15 blade was used to make the initial scalloped internal bevel incision starting apical to the points that marked the course of the pockets including the new interdental papillae [Fig 4 &5].

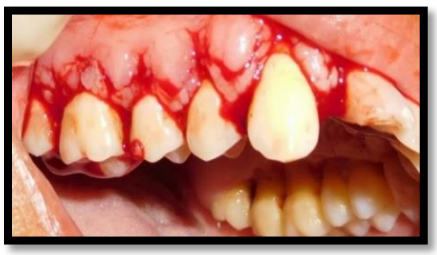

Fig 4: Internal bevel incision

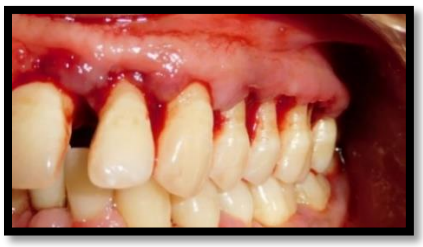

Fig 5: Crevicular incision given & adaptation after excision of enlarge tissue in maxillary arch

A point apical to the alveolar crest was used to make the incision. In addition to the initial incision in the buccolingual direction up to the mucogingival junction, the flap was thinned. Enough attached gingiva was retained after the removal of the pocket wall.

A crevicular incision from the bottom of pocket to the bone was made. Then an interdental incision was used to separate the bone and connective tissue, and curettes were used to remove the triangular wedge of tissue that had been created.

The flaps were put on the position of root-bone junction after scaling and root planing. Black braided 3-0 silk sutures were used to place interrupted sutures [Fig.6&7].The patient was given postoperative medications and instructions.

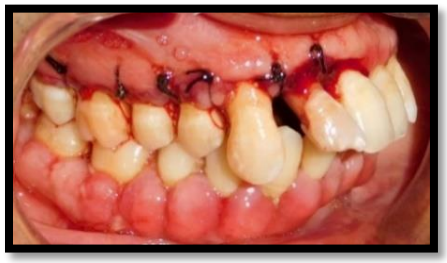

Fig 6: Post-operative sutures in right maxillary arch

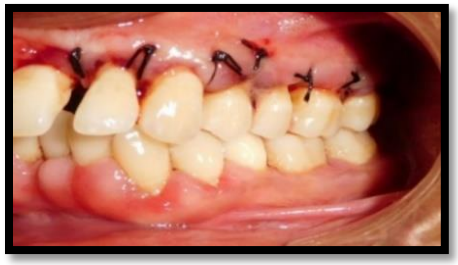

Fig 7: Post-operative sutures in left maxillary arch

After seven days, sutures were removed and the healing was uneventful. Both the upper and lower arches underwent the same procedure with a gap of seven days between two periodontal surgeries. Due to adequate plaque control, there were satisfactory post-operative results three months later [Fig 8 and 9].

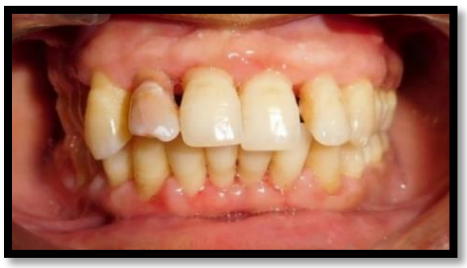

Fig 8: 6 month Post-operative facial view

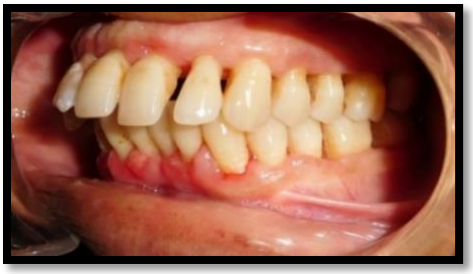

Fig 9: 6 month Post-operative view of left side

The excised tissues were sent for a histopathological examination. Gingival hyperplasia showing hyperplastic epithelium with thin elongated rete pegs penetrating deep into the connective tissue was revealed upon microscopic examination of soft tissue specimen. Dense collagen fiber bundles, blood vessels, and chronic inflammatory cells were shown by the connective tissue. There is no malodor and there is a significant improvement in the patient's quality of life due to the improved aesthetics and oral hygiene maintenance.

Discussion

Enlargement of the soft tissues surrounding the teeth often accompanies the administration of diphenylhydantoin (Phenytoin; PHT) on a long term regimen for control of grand mal seizures.[6] The condition is often called phenytoin-induced gingival enlargement (PIGE). The result of gingival enlargement, the pseudopockets, increase plaque retentive areas, further predisposing the patient in the direction of an enhanced awareness for changes in the gingiva, dental caries and periodontal diseases.[7]

About 30 to 50% of patients that take PHT develop significant gingival alterations.[8] Other anticonvulsants, including sodium valproate, phenobarbitone, vigabatrin and primidone, have been associated with gingival enlargement as well. There have rarely been any reports of gingival changes in adult patients that use these drugs long-term.[9] Some of the common clinical symptoms, such as hindrance during speech and mastication, occlusion difficultly, unpleasant appearance, malalignment of teeth, increased frequency of caries, occlusion difficulty, and developmental of periodontal diseases, accompany gingival enlargement. The association between PHT and gingival enlargement has existed for decades.[10]

Many etiological factors may result in fibrotic enlargement; this is called gingival overgrowth. This disease may worsen due to dental biofilm; sometimes, the disease may be a side-effect of systemic medications or other systemic disease may be associated with it.[11] Correa et al.[8] suggested that the mechanism of gingival overgrowth resulting from decreased collagen degradation may involve changes in calcium metabolism, integrin expression, and levels of MMPs and TIMPs. Kato et al.[12] showed reduced expressions of genes encoding collagen types 1 and 3 combined with a density that was higher in gingival overgrowth fibers. They proposed than an imbalance in collagen degradation, not an increase in collagen synthesis caused PIGO. In another study,[13] they suggested that a relationship between tumor necrosis factor – alpha (TNF-α) production and the phenytoin that human gingival fibroblasts contain might exist. The results suggested that collagen metabolism was caused by TNF-α and phenytoin combined, resulting from enzymatic degradation by MMPs (matrix metalloproteinases)/TIMP-1 (tissue inhibitor of metalloproteinases) and integrin mediated endocytosis, which may lead to collagen accumulation during gingival overgrowth.

In 1977, Angelopoulos[14] conjectured that end-organ folic acid deficiency caused phenytoin induced gingival enlargement. This could cause the inflammation-susceptible gingival tissue because of degenerative changes in local irritants' main physical barrier, the gingival sulcular epithelium.

PHT has been used for the majority of the studies evaluating pathogenesis of DIGE involving anticonvulsants.[10] The clinical and microscopic appearance of DIGE caused by any drug is similar although the mechanism of action may not be.[15] It starts as a nodular and firm enlargement of the interdental papilla, within three months of using drugs such as PHT, which is restricted to keratinized portions of the gingiva. The target cell is the gingival fibroblast since all lesions display an increase in the component of the connective tissue.[16] Several of the clinical features of this case are also alike.In review of drug induced gingival overgrowth's pathogenesis performed by Seymour et al, the risk factors considered contain the following: sex, age, periodontal variables, drug variables, genetic factors, and concomitant medication.[17] The existence of plaque is like a cofactor in DIGE's etiology. In this situation, the presence of severe gingival inflammation was also observed.

Determinants in DOGE's pathogenesis include the gingival binding affinity of inducing drugs and their pharmokinetics.12 According to a recent study, the modification of the inflammatory response to PHT is caused by CYP2C9 gene polymorphism.[18]

The review of many investigators into DIGE's pathogenesis supports the hypothesis that it is a side effect with a multifactorial etiology. The communication between fibroblasts and drugs seems to be coordinated by the inflammatory changes that happen inside gingival tissue.[8] IgA salivary level reduction is also the cause of phenytoin induced gingival enlargement although this has not been confirmed, as well as sub-gingival microflora's alteration.[8]

Various modalities used to treat such enlargements are scalpel, electrosurgery, lasers, and crysosurgery.[19] This report showed that an improvement in manifestations with a considerable reduction in gingival overgrowth

after a number of appointments for scaling, root planing and reinforcement of oral hygiene instructions. In the absence of any attachment loss, electrocautery and lasers have proven to be the best modalities to treat the enlargement,[20] due to their advantages of hemostasis and lesser post-operative pain and discomfort. In current case as attachment loss with true pockets was present at almost all the sites, internal bevel gingivectomy was chosen as the treatment option to excise the growth and flap was reflected to debride the root surfaces properly. If any need for gingivoplasty remains to correct any residual enlargement even after surgery, the same can be done after 3-4 weeks of surgery using scalpel, electrocautery or laser. In the present patient, considerable improvement in gingival contour and pocket depths was seen after surgery precluding any need for further corrective surgery.

Conclusion

The reported case is an example of slowly progressive periodontitis. This was superimposed by a combined type of gingival enlargement; basically a drug induced one, complicated by inflammatory changes due to plaque accumulation.

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