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Drug Induced Gingival Enlargement-A Case Report

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Abstract:

Gingival Enlargement is a side effect associated with some distinct classes of drugs, such as anticonvulsants, immunosuppressant, and calcium channel blockers. Gingival overgrowth 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 Gingival overgrowth is the antiepileptic phenytoin, which affects gingival tissues by altering extracellular matrix metabolism. , the degree of gingival enlargement in patients receiving anti-convulsing treatment is well correlated with poor plaque control. In fact, the 2014 classification system for periodontal diseases stated that plaque represents a cofactor in the etiology of drug-induced gingival overgrowth. Moreover, the gingival enlargement could make plaque control difficult, leading to a secondary inflammatory process, which aggravates the overgrowth induced by the drug. A 35 year old female patient was reported to OPD with complaints of gingival enlargement. History dates back to 6 months, patient noticed mass present on upper left gum region which was gradual in onset, continuous on progress, initially small in size and increased in size to attain present size and also felt excessive salivation. Patient is epileptic and has been taking the drug phenytoin sodium (100mg BID) for seizure control approximately since 13 years .Seizure occurred when patient stop taking medication. We advised to maintenance of strict oral hygiene used regular mouth wash using chlorohexidine, and surgical excision. Recurrence may occur as early as 3 to 6 months after surgical treatment. The patient was under regular follow up and wound site healed without any further complications.

Keywords:	*Gingiva, Phenytoin, Antiepileptic, chlorohexidine*
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1. Introduction

Drug-induced gingival overgrowth is more commonly seen in male children and adolescents with a more prevalent location in the anterior gingival tissue. Genetic heterogeneity also plays a vital role, and the extent and degree of overgrowth depend on

the drug. Phenytoin, cyclosporin, and nifedipine are the most common causes of gingival overgrowth, and phenytoin has the highest prevalence of all. It is estimated that 50% of adults treated with phenytoin experience gingival enlargement, 30% with cyclosporin, and 20% with nifedipine.[1]Most common Anticonvulsants drugs are:- Phenytoin, Sodium valproate, Phenobarbitone, Vigabatrin, Primidone, Mephenytoin, Ethotoin, Ethosuximide, and Methosuximide. Most common Immunosuppressants are Cyclosporin, Tacrolimus, Sirolmius. Most common calcium channel blockers are Nifedipine, Nitrendipine, Felodipine, Nicardipine, Manidipine, Amlodipine, Nimodipine, Nisoldipine, Verapmil, and Diltiazem. Erythromycin: A single case of gingival overgrowth has been associated with the use of erythromycin in a young boy (Valsecchi and Cainelli, 1992).[1] .A correlation with dosage, duration, drug concentrations and severity/extent of gingival enlargement has also been suggested, but so many variables can influence this aspect, that it remains controversial. However, it has been recently reported that patients treated with ciclosporin solution experience earlier onset of gingival changes and more extensive overgrowth than patients using capsules. Studies have demonstrated that patients developing gingival lesions have high frequency of particular HLA antigens and genetic markers (cytochrome P450, HLA-DR2,) and this appears to be related to a genetic predisposition for this pathology. It has also been reported that patients who expressed genetic markers such as HLA-B37or HLA-DR1, are afforded some degree of protection against gingival overgrowth.[2] The pathology lies in the connective tissue and not the epithelial cells of the gingiva. There is an excessive accumulation of extracellular matrix-like collagen with varying amounts of inflammatory infiltrates, predominantly plasma cells. Fibroblastic proliferation may not be evident. Erratic columns of collagen fibers are seen interspersed with penetrating epithelial ridges.[3]

In this case report, we present a case of Phenytoin sodium induced chronic maxillary papillary gingival overgrowth in a epileleptic patient.

2. Case Report

A 35 year old female patient reported Private Dental Clinic complaints of growth on upper left back jaw region since 6 months, and also complains of bleeding gums. History dates back to 6 months patient noticed a mass present on upper left gum region which was gradual in onset, continuous on progress, initially small in size and increased in size to attain present size. There is no pain in swelling but foul smell, excessive salivation, and bleeding during tooth brushing is present. Patient brushes twice in a week & overall poor oral hygiene. Past medical reports showed that Patient is epileptic (grand mal type) & has been taking the drug phenytoin sodium(100mg BID)for seizure control approximately for the past 13 years .Seizure occurred when patient stop taking medication. Last epileptic seizure occurred 1 month back.

General physical examination revealedthat Patient was conscious, asthenically built, cooperative and well oriented to time, place & person. Patient was afebrile with pulse rate- 77 beats/min, respiratory rate- 18 breaths/min & blood pressure- 110/80mm of Hg. No signs of pallor, icterus, cyanosis, edema, anemia & clubbing.No abnormalities detected on extra-oral examination.

Intra oral Clinical examination on inspection revealed that there was gen. gingival enlargement, which was pale pinkish in color, firm in consistency, Increased in size having blunt contour and loss of stippling. In region 26 ; Solitary well defined, reddish pink lobulated gingival growth with sessile base was present on buccal aspects of marginal gingiva to involve attached gingiva The growth has max dimensions of 2x1.5 cm in size. On palpation all the inspectory findings were confirmed regarding size, shape & extent & it was firm in consistency, non-tender, mobile 26.On probing, pseudo pockets were found 26, with 5mm ,4.5mm in lengths; no pockets were present all other teeth and bleeding on probing was not probing in all teeth. (Figure 1)

Hematological Investigations was Red blood cells: 4.2 million (3.8-5.3 million)/mm^3,Hemoglobin: 11.9mg/dl (12-18) mg/dl,Total Leukocyte count: 8800(4200-10000)/mm^3, Differential leukocyte count, Neutrophil : 65 (60-70%), Lymphocytes:32 (20-40%) ,Monocytes:02 (2-6%),Eosinophil-01(1-4%), Basophil-00 (0-1%), Granulocytes: 4.5x10^3/µL (4200-8500)/mm^3, Platelets: 84x10^3/µL (150000-450000)/mm^3 , Erythrocyte sedimentation rate: 9mm/1hr (0-10mm/hr), Blood sugar: 77mg/dl (70-150) mg/dl, Bleeding time: 3.05(2-4min), Clotting time: 4.30min (6-8) min, SGOT- 42(8-40 IU/L), SGPT: 44.2 (10-40 IU/L).Provisional diagnosis were Drug induced Gingival Enlargement and Chronic generalized periodontitis. Differential diagnosis were Epulis, Pyogenic granuloma, Irritatonal fibroma.

Excisional biopsy was done and specimen was sent for histopathological examination (10x, H&E stain) (Figure) which shows parakeratinised stratified squamous epithelium with elongated deep rete-pegs with deep into connective tissue, which exhibits densely arranged collegen bundles. Severe inflammatory cell infilteration consisting of lymphocytes & plasma cells are noticed in the stroma. Extravasted RBC are present in same area of section.

Based on the history ,clinical examination & histopathological examination, a confirmatory diagnosis was drug induced gingival hyperplasia with Chronic generalized periodontitis .Patient was under regular follow up and advise to maintain the oral hygiene and replace the medication if possible for some time under the observation of physician.

3. Discussion

Diagnosis is very important in medically compromised patients as it is extremely difficult to treat oral problem when systemic diseases are the main problem. In 1996, Seymour et al. postulated the theory of genetic predisposition for the etiopathology of Drug Induced Gingival Overgrowth. This is substantiated by the fact that some individuals develop gingival hyperplasia and some do not whilst on the same drug. The usual inflammatory response of gingival fibroblasts and subsequent proliferation of connective tissue matrix emphasizes the heterogenetic character of the individual's gingival fibroblasts in response to the inducing drugs. The common mechanism of action at the cellular level of all these three categories of dissimilar drugs appears to be inhibition of cation influx, particularly sodium and calcium ions.Inducing drugs act as a trigger for the activation and proliferation of gingival fibroblasts, causing an increased connective tissue production of GAGs (glycosaminoglycans). These drugs decrease cellular uptake of folate by genetically predispose fibroblasts. Reduced

intracellular folate translates into a decrease in the synthesis or activation of MMPs (matrix metalloproteinases), which are required to convert inactive collagenase to active collagenase, allowing an excess of connective tissue build up. Brown et al. (1991) postulated that bacterial plaque contributes to gingival inflammation, which completes the vicious cycle.

Matrix Metalloproteinases: more than 20 enzymes that bring about the degradation of connective tissue and tissue remodeling. These include collagenases, gelatinases, and stromelysins. Inhibition of activation of these can result in the accumulation of extracellular matrix and collagen and cause drug induced gingival overgrowth.

Kantarci *et al*. demonstrated that there are significantly higher numbers of basement membrane discontinuities in overgrowth tissues, sometimes containing epithelial-like cells. Disrupted basal membrane structure in gingival overgrowth tissues is accompanied by a discontinuous collagen type IV expression pattern and decreased laminin-5. These findings provided a new additional support for the hypothesis that epithelial plasticity and epithelial to mesenchymal transition promote gingival overgrowth, resulting in compromised basal membrane structure and increased interactions between epithelial and connective tissue layers that contribute to fibrotic pathology.

Subramani *et al*., observed that mast cells participate in many inflammatory oral diseases, particularly those associated with fibrosis. They possess very diverse roles ranging from proinflammatory to immunomodulatory. Upon their activation, they promote the local renin angiotensin system generation consequently able to stimulate endothelin and other profibrotic mediators. Cyclosporin can modulate local expression of renin angiotensin system components such as angiotensinogen, angiotensin II and its receptors in gingival tissues, and gingival fibroblast cells.[3]

Inflammatory Cytokines: Inflamed gingival tissue exhibits higher levels of interleukin-1 beta (IL-1beta), a proinflammatory cytokine. Likewise, IL-6 causes fibroblastic proliferation and increased production of collagen and GAG synthesis.

Na+/ Ca2+ ion Flux Drug Mechanisms: Fugi and Kobayashi (1990) reported inhibition of Ca2+ uptake within gingival fibroblasts by PHT and several calcium channel blockers (CCBAs). Thomas and Petrou (2013) reported a reduction in Na+ channel availability and, therefore, a decrease in the action potential amplitude. This causes reduced Ca2+ entry, and a decrease in Ca2+ activated K+ channels. All three types of DIGO-inducing drugs act on Ca2+ flux similarly.

Plaque Buildup: The concentrated drug in crevicular gingival fluid or bacterial plaque exerts a direct toxic effect on the gingival tissue. Dental plaque induces inflammation, which causes gingival overgrowth. Inflammation causes the upregulation of transforming growth factor-beta 1 (TGF-beta 1). Hence, control of dental plaque is needed in the treatment and prevention of DIGO over time.[1]

Phenytoin (PHT; 5,5-diphenylhydantoin) was first introduced as an antiepileptic drug in 1938. Vigabatrin is a relatively new antiepileptic agent that can also cause gingival overgrowth.. Phenytoin was first reported to associated with chronic gingival overgrowth 1939 by Kimball. In 1959, Strean & Leoni - alkalinity of phenytoin might be the cause of the gingival side effect..In 1948, Brandon - phenytoin had a direct action on the gingival tissues. In 1975,

Angelopoulos argued that phenytoin induced degranulation of mast cells .Larmas, in 1976, suggested that phenytoin had a proliferating effect primarily on the basal cell layer of the oral epithelium thus increasing the epithelium-connective tissue interface area .

Immunohistochemical study suggested that vigabatrin induced an increase in epithelial cell proliferation due to overexpression of antigen Ki-67 and slight underexpression of the CDK-inhibitors $p27^{KIP1}$ and p21.Administration of multiple anticonvulsants in children also has an additive effect on gingival overgrowth. PHT, primidone, and phenobarbitone are all metabolized to 5-(4-hydroxyphenyl) 5-phenylhydantoin (4-HPPH). The increased serum concentration of this metabolite might explain the additive effect of multiple anticonvulsant therapy to gingival overgrowth.Other drugs known to induce gingival overgrowth include are ethotoin, mephenytoin, ethosuximide, methosuxinimide. Cyclosporin is a powerful immunosuppressant widely used for prevention of transplant rejection as well as for management of a number of autoimmune conditions. However, cyclosporin may have damaging side effects, such as nephrotoxicity, hepatotoxicity, hypertension, and gingival overgrowth.

The first time gingival overgrowth with cyclosporin therapy was described in the dental literature in 1983 by both Rateitschak-Plüss *et al*., and Wysocki *et al*. Recently, Greenberg *et al*. studied a sample of 115 patients that underwent kidney transplants and found a gingival overgrowth prevalence of 53% among those who were treated with cyclosporin.

Tacrolimus or FK506, is a macrolide molecule which has been shown to have major potential as an alternative immunosuppressant to cyclosporin. Tacrolimus has similar side effects when compared with cyclosporin, but where gingival overgrowth is concerned, the results appear to differ. It is also nephrotoxic, but it results in much less severe hypertension and hypertrichosis. Various studies have demonstrated less frequent association of gingival overgrowth with the use of tacrolimus than with cyclosporin. Synergistic effects have been reported when cyclosporin is administered concurrently with calcium channel blockers of dihydropyridine derivatives.

Furthermore, gingival overgrowth is also demonstrated in transplant subjects under sirolimus based regimens, but within a nonsignificant clinical threshold. Antihypertensive drugs in the calcium channel blocker group are used extensively in elderly patients who have angina or peripheral vascular disease. The first case of nifedipine-induced gingival enlargement was reported in mid 1980s by Lederman *et al*., and Ramon *et al*., and was soon also described with diltiazem, verapamil, and in cases with amlodipine and felodipine. Ikawa K *et al*.,presented a case report of severe gingival overgrowth induced by manidipine in a female patient. The choice of the calcium channel blocker used in conjunction with cyclosporin can also affect the prevalence or severity of gingival enlargement. It has been reported that the prevalence of gingival overgrowth in renal transplant recipients maintained on cyclosporin and amlodipine is higher than those receiving cyclosporin and nifedipine.[1]

Rashi Chaturvedi , Ashish Jain conducted a clinical presentation of a series of five cases in the age range of 45-65 yrs with gingival over-growth as a side effect of therapy with amlodepine is presented with prescription of variable doses of 2.5 mg, 5 mg and 10 mg

per day. A brief review on the pathogenesis of this condition, commonly associated etiological mechanisms and sequence of periodontal therapy rendered have also been included. They concluded that Irrespective of the dose of amlodepine administered, gingival enlargement continues to be a predominant side effect in all of the five cases presented. The accentuated gingival contours accumulate plaque leading further to the destruction of the underlying periodontium. Dental professionals need to identify and then guide the patient to seek necessary medical intervention.[4.]

In addition, when effects of a combined treatment of cyclosporin and nifedipine or diltiazem were tested in an animal model, cyclosporin was found to synergistically enhance gingival growth with nifedipine and to a lesser degree with diltiazem.[1]

Lauitano D et al in a study compared the effects of diphenylhydantoin and gabapentin on 57 genes belonging to the "Extracellular Matrix and Adhesion Molecule" pathway, present in human fibroblasts of healthy volunteers. Results. Both molecules induce the same gene expression profile in fibroblasts as well as a significant upregulation of genes involved in extracellular matrix deposition like COL4A1, ITGA7, and LAMB3. The two treatments also induced a significant downregulation of genes involved in the expression of extracellular matrix metalloproteases like MMP11, MMP15, MMP16, MMP24, and transmembrane receptor ITGB4.They concluded and confirmed the hypothesis of a direct action of these drugs at the periodontium level, inducing an increase in matrix production, a reduction in its degradation, and consequently resulting in gingival hyperplasia.[5]

A correlation with dosage, duration, drug concentrations (in blood and whole saliva) and severity/extent of gingival enlargement has also been suggested, but so many variables (sampling technique, pharmacokinetic factors) can influence this aspect, that it remains controversial. However, it has been recently reported that patients treated with ciclosporin solution experience earlier onset of gingival changes and more extensive overgrowth than patients using capsules.[2] Phenotyoin gingival overgrowth can occur early within 3 months of the drug use and it may reach a state of equilibrium often within the first year of the beginning of medication .[6]

Right diagnosis at the right time could be life saving for the patient. We are proud that the patient could be identified promptly and relieved of his oral problems without much post-operative morbidity.

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Figures with Legends:

Figure 1 showing papillary gingival overgrowth in posterior region.

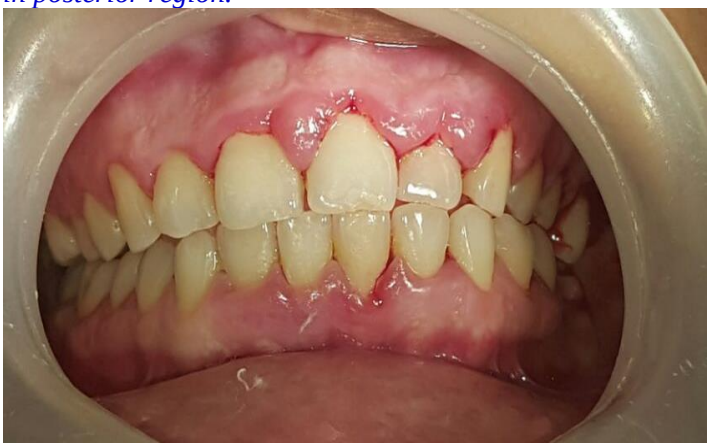

Figure 2 showing interdental papillary gingival overgrowth in anterior region of maxilla.

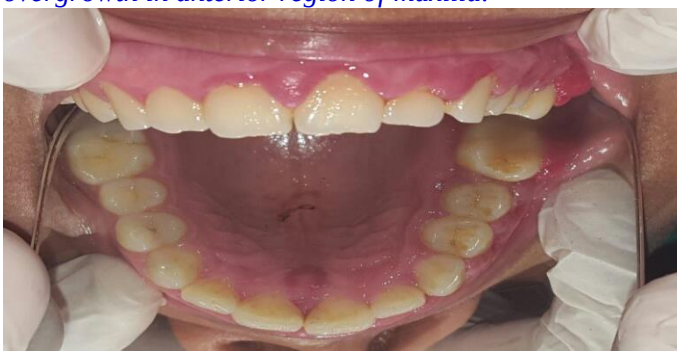

Figure 3 showing lingual view of mandibular gingiva

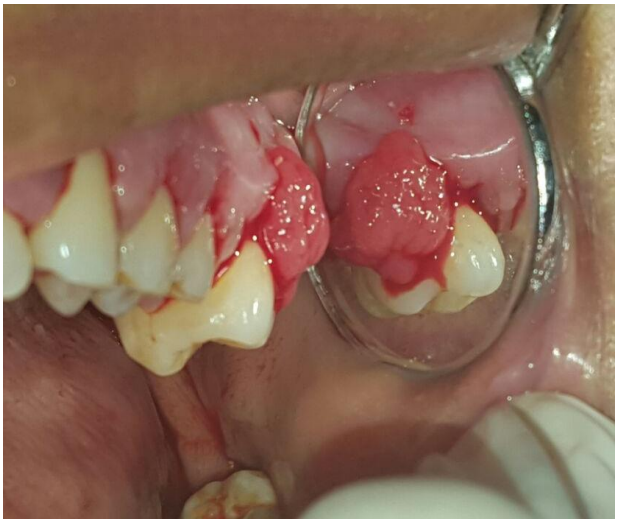

Figure 4 showing perfuse bleeding from gingivalgrowth

Figure 5 showing punch biopsy procedure

Figure 6 showing tissue in 10% Formoline after excision

Figure 7 Showing histological view of gingival overgrowth (10X)