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DRUG INDUCED GINGIVAL ENLARGEMENT

Devesh D. Gosavi, Sanjay Nanotkar and Akanksha Suman

Dept Of Pharmacology, MGIMS , Sewagram, Wardha , Maharashtra, India

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ABSTRACT

Gingival enlargement is an abnormal growth of the periodontal tissue. Several causes of gingival enlargement are known, and the most recognized is drug-induced (iatrogenic) gingival enlargement (GE) . Antiepileptic **(**Phenytoin PNT), Immunosuppressant (Cyclosporin A), Calcium channel blockers (Nifedipine) are implicated.
GE is the most common ADR in the young adults and children receiving PNT as antiepileptic therapy. Though poor oral hygiene and dental plaque are considered important risk factors in pathogenesis of GE, meticulous oral hygiene can minimize but not prevent the occurrence of GE. Pathogenesis is multifactorial and seems to be a modulation in inflammatory response i.e. exacerbation of the normal tissue turnover / healing signals by PNT. The most effective treatment of drug-induced gingival enlargement is withdrawal or substitution of medication i.e. PNT. Antimicrobials are found useful in alleviating the symptoms of GE. Considering alternatives to PNT 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

Key words: Gingival enlargement, Phenytoin, Dental Plaque.

INTRODUCTION:

Definition: Gingival enlargement is an abnormal growth of the periodontal tissue. Several causes of gingival enlargement are known, and the most recognized is drug-induced (iatrogenic) gingival enlargement (GE) [(1)].
Following drugs are implicated:
Antiepileptic**:** Phenytoin (PNT), Phenobarbital [(1, 2)]

Immunosuppressant: Cyclosporin A Calcium channel blockers: Nifedipine, Amlodipine.

Other causes of gingival enlargement being leukemias, Wegener's granulomatosis, and malignant melanoma [(1)].
The condition was first reported in dental literature in early 1960`s in the children who were receiving phenytoin (PNT) as antiepileptic therapy.

EPIDEMIOLOGY: There is no ethnic, racial or genetic predilection. The factors affecting the

occurrence of GE may include gender, with males being three times as likely to develop overgrowth (GE) [2]. Children & adults younger than 30 yrs of age are more susceptible [2]. Roughly 50 % of the patient on PNT therapy develops this ADR within 1 year of commencing therapy and is probably the most common ADR in children and young adults receiving PNT [1, 2].

RISK FACTORS: As not all patients on phenytoin (PNT) therapy develop this, there is the need to identify risk factors involved [1, 2].The adverse effects of PNT depend on the duration of exposure, and the dosage. The other risk factors are poor oral hygiene, poor socioeconomic class and poor educational status. Dental plaque, as it acts as a reservoir for accumulation of drug, is commonly associated with this condition [3]. The local risk factors are mal-positioned teeth, gingivitis and mouth breathing. Physical irritants like orthodontic appliances, implants, filling also play their role in the causation of this ADR [1].

In our ongoing study of adverse drug reactions due to AED (antiepileptic drugs) it is found that, out of 15 patients on PNT, 2 patients develop GE. One of the patients was on PNT therapy for one year. After 9 months, he developed anterior maxillary GE. The laboratory finding coinciding with the occurrence of GE was serum conc. of PNT being 6.2mcg/ml which is well within normal limits. Apart from GE, sedation was experienced.

Another patient on PNT since 2 years developed GE after 1 ½ years of therapy, involving upper gums. Other associated complaints were giddiness, ataxia, and increased seizures. Serum concentration of PNT found to be 29.61mcg/ml which falls in toxic range.

PHARMACOKINETICS OF PNT: Among the causes for drug induced GE, PNT is the most common agent [1, 2]. It is widely distributed in all the body fluids including CSF. It is also secreted in saliva and dental plaque acts as a reservoir for the drug [1, 3]. Drug concentration in cerebrospinal fluid is proportionate to its free plasma level. PNT accumulates in brain, liver, muscle, and fat. Its metabolism gets saturated and its rate of elimination varies as a function of its concentration (*i.e.*, the rate is nonlinear). The plasma $t_{1/2}$ ranges between 6 and 24 hours at plasma concentrations <10 μg/ml but increases with higher concentrations. As a result, plasma concentration increases disproportionately even with the small increments in the dose.

PNT is largely (95%) metabolized by hepatic CYPs (CYP 1A1, 1A2, 2C9, 2E1, 3A4). The principal metabolite, a para-hydroxyphenyl derivative 5-(4Hydroxyphenyl)-5-phenylhydantoin (HPPH), is excreted in urine [4]. Only a very small portion of PNT is excreted unchanged. About 98% of circulating HPPH is in the (S) form and the remaining is in (R) form. R-HPPH, although least abundant metabolite, appears to be more toxic and stimulates fibroblast growth. The formation of HPPH, locally in the gingiva is due to presence of one or more CYPs, which can cause cell injury and activates inflammatory response and fibroblastic proliferation [5, 6].

PATHOGENESIS: 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 [1, 2]. 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 differentiation [1, 2]. The condition appears to be a result of interaction of susceptible subpopulation of fibroblasts, keratinocytes and collagen with PNT & its metabolite [2, 3]. There is a possible role of various growth factors like platelet derived growth factor (PDGF), transforming growth

factor (TGF), connective tissue growth factor (CTGF) and cytokines (IL-1β) [1, 2].

After being secreted through saliva, the active metabolite of PNT inhibits cellular uptake of folate and folate depleted cells can't synthesize enzymes necessary for breaking down the extra connective tissue [7] leading to matrix deposition. PNT also increases the expression of the gene for platelet derived growth factor –β (PDGF-β), transforming growth factor-β (TGF-β) and their m-RNA [8, 9]. These two factors increase CTGF-Connective tissue growth factor which causes persistent proliferation of connective tissue, matrix formation and fibrosis [8, 9, 10]. PDGF, TGF also increases lysil oxidase activity which is utilized in the final enzymatic step of collagen cross linking and thereby causes ECM accumulation [8, 9, 10, 11,12]. (fig.2)

Matrix metalloproteinases (MMP`s) because of their major role in cellular proliferation, migration, differentiation, and angiogenesis might play a role here also [13, 14].

The histopathology reveals following features: [1]

1. Highly vascular connective tissue with focal accumulation of inflammatory cells primarily plasma cells and Langerhans cells.
2. The overlying epithelium is of varying thickness, irregular and is multilayered.
3. Acanthosis, parakeratocytosis with pseudoepitheliomatous proliferation.
4. Hyperplastic tissues reveal presence of myofibroblast with abundant cytoplasmic rough endoplasmic reticulum, polyribosomes and collection of subplasmalemmal microfilaments containing spindle densities [15, 16].

Altogether the pathogenesis seems to be a modulation in inflammatory response i.e. exacerbation of the normal tissue turnover / healing signals by PNT.

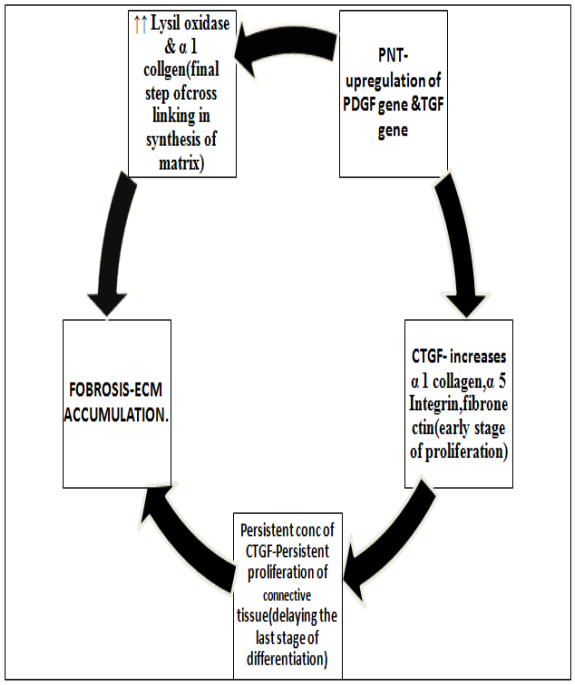

Figure 1:

GROSS: GE produces a firm pink growth; but in superimposed gingivitis and periodontitis, it may cause gingiva to become boggy and red or purplish in color. GE occurs primarily on the anterior, labial gingival mucosa, interdental papillae [17]. This is more pronounced on labial maxillary gingiva; the less affected being the posterior lingual gingival mucosa [1, 2]. For reasons unknown, it is rarely seen in edentulous areas [18].

PROGRESSION: Onset of GE in susceptible individuals is insidious. It develops within 2 wks to 3 months of the initiation of therapy, being most pronounced in the first year [19]. GE is asymptomatic to start with. As the tissue enlarges, the overgrowing mucosa may cover tooth surface, including the occlusal (chewing) surface as well as extending other ways to sulcus. The condition may progress to be a cosmetic problem, interfere with eating, speech, painful at

times, impede effective tooth cleaning or force the tooth out of alignment [18].

SYMPTOMS: GE presents as enlarged gums, loosened tooth and change in the tooth alignment. Sometimes the patient may present with the symptoms of complications.

Complications: Bleeding gums due to trauma to the soft tissue, suppuration and halitosis due to inadequate cleaning of the tooth and early tooth loss because of severe GE and loosening and misalignment of dentures.

INVESTIGATIONS:

1. Complete hemogram: patient with severe gum bleeding to rule out any hematological cause (leukemia) or complication (anemia due to bleeding gums).
2. Liver function tests for increased transaminases.
3. Plasma, serum and salivary concentration of the PNT.
4. Culture – to rule out oral candidiasis.
5. Tissue biopsy –in an unusual presentation of gum overgrowth.
6. Imaging – Periapical (full mouth series) or Panorex (panoramic view) prior to treatment to evaluate the status of periodontal tissue or any compromised teeth [1].
7. Perio dontal examination.

TREATMENT:

The management of GE is essentially multidisciplinary which includes medical, surgical and supportive care.

MEDICAL CARE:

The most effective treatment of drug-induced gingival enlargement is withdrawal or substitution of medication i.e. PNT [20]. Unfortunately, not all patients respond to this mode of treatment, especially those with longstanding gingival lesions [2, 21].

A) Antimicrobials: These are used for the treatment of GE and associated infections like periodontitis. But some of them are interfering with collagen synthesis and breakdown also.

1. **Macrolides-** Azithromycin, Roxithromycin: Arrests GE by inhibition of expression of gene for collagen type 1 leading to decreased protein synthesis. Also there is up regulation of mRNA for MMP -2, a cell surface associated type 1 collagen degrading MMP causing increased degradation of collagen. It is also thought to reduce the viability of gingival fibroblast as it blocks the DNA synthesis. [22,23,24].
2. **Tetracyclines-** Doxycycline/Minocycline- inhibits specific MMP`s required for collagen synthesis. [25]

B) Antiseptic mouth wash-

I. Chlorhexidine gluconate-
II. Biotene (Lysozyme, lactoferrin, glucose oxidase, lactoperoxidase)

C) Folic acid 1 mg one to three times a day is to be supplemented to take care of PNT induced folate deficiency.

SURGICAL CARE: This option is sought in moderate to severe cases, not resolving even after decreasing the dose of the offending drug, maintaining proper oral hygiene, not responding to professional debridement with scaling or root planning. It includes Flap procedures [1] which clean the root of a tooth and repairs bone damage caused by gum diseases. The other option is Gingivectomy. If carried out with routine surgical methods, there is rapid recurrence [2, 9]. Hence the preferred method is the use of CO2 or YAG Laser [1, 2], an approach which provides rapid postoperative hemostasis.

SUPPORTIVE CARE: This involves informing patients of the risk of developing GE secondary to PNT therapy and the role of oral health in minimizing complications.

Routine dental examination is recommended to control development of dental plaque. As presence of plaque predisposes to GE, removal of

plaques, calculus deposits often reduces mild and moderate GE thus avoiding surgical intervention.
Proper cleaning (brushing and flossing) of each tooth separately is must. Patients should practice thorough oral hygiene twice a day (i.e., before breakfast, before going to bed) and rinse mouth with plain water after each meal.
Tooth staining due to mouthwash is an anticipated side effect. It can be prevented by brushing teeth prior to rinsing out with chlorhexidine.
No dietary restriction as such are there for preventing GE but once it ensues; one should minimize sweets, carbohydrates, soft drinks.

PROGNOSIS: The condition has a better prognosis if patients maintain regular oral hygiene and plaque control.

SPECIAL CONSIDERATIONS:

1. Many cases of GE will respond to local treatment i.e. scaling and root planning. But if it poses considerable trouble to the patient i.e. enlargement covers more than about a third of the tooth surface, one should consider substituting the drug if dose reduction is not possible in an individual case. This approach may bring about partial or complete regression of the lesion. Most patients will observe an alteration in the soft tissues within a few days [(18)].
2. Several alternatives to PNT are available, but they may not be as well tolerated or they may not control seizures as well. Recently, the feasibility of phenytoin substitution has increased with the addition of a new generation of anticonvulsants such as lomatrigine, gabapentin, carbamazepine and topiramate. Some patients can switch to a lower dose of PNT combined with another anticonvulsant.
3. There is every possibility of recurrence of GE despite periodontal treatment if a person continues taking the same offending medication [(18).]
4. Discontinuance of PNT therapy may result in gradual regression of the lesion over the time [(26).]
5. Dental plaque is not essential for the development but related to its severity, though not all the patients with poor oral hygiene develop this [(26)].

CONCLUSION: GE is the most common ADR in the young adults and children receiving PNT as antiepileptic therapy. Though poor oral hygiene and dental plaque are considered important risk factors in pathogenesis of GE, meticulous oral hygiene can minimize but not prevent the occurrence of GE[(2)]. Antimicrobials are found useful in alleviating the symptoms of GE. Considering alternatives to PNT 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 GE and thereby providing novel information for future preventative and effective therapeutic modalities.

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Photograph showing GE