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Phenytoin-induced gingival overgrowth: A case report



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ABSTRACT

Drug-induced gingival enlargement manifests as an abnormal growth of the gingiva due to an adverse drug reaction in patients treated with anticonvulsants, immunosuppressants and calcium channel blockers. The enlargement affects the normal oral hygiene practice and may even interfere with masticatory functions. It may gradually becomes a source of pain and could lead to disfigurement and cosmetic problem, interfere with mastication and speech, impede effective tooth cleaning or force the teeth out of alignment.

It is a serious concern for both the patient and the clinician due to unaesthetic appearance and formation of new niches for Periodonto-pathogenic bacteria. Among the anticonvulsants, Phenytoin has most frequently been described to be associated with Gingival Enlargement. This case report presents gingival hyperplasia as a side effect of Phenytoin use in a 17-year-old female patient on this drug for the last 1 year.

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1. Introduction

Drug-induced gingival overgrowth occurs in whole or in part from systemic drug usage. It occurs as a side effect following the administration of drugs used mainly for non-dental treatments and thus, the overgrowth can not be explained as a variation of the intended pharmacological action of the drug.[1] Several factors namely; age, genetic predisposition, presence of preexisting plaque, and gingival inflammation influence the relationship between the drugs and gingival tissue.[2] Gingival enlargement may create speech, mastication, tooth eruption and esthetic problems.[3] Currently, more than 20 prescription medications are associated with gingival enlargement. Drug-induced gingival overgrowth usually occurs within the first 3 months of starting the medication and begins as an enlargement of the interdental papilla.[3] As mentioned elsewhere, not all patients taking these drugs develop drug-induced gingival overgrowth. While the incidence of this side effect can be as high as 65% in epileptics, 70% in transplant patients, and 30% in hypertension subjects, variation exists in the reported prevalence and severity of the clinical problem.[4,5]

Anticonvulsants are used in the management of various seizures like Tonic clonic seizures, Petit Mal seizures etc. These drugs have been reported to be associated with gingival hyperplasia since long.[6] Of this large group of drugs, the diphenylhydantoins are most frequently implicated in gingival enlargement especially Phenytoin. Phenytoin (PHT; 5, 5-diphenylhydantoin) was first introduced as an anti-epileptic drug in 1938. It is slowly absorbed from the gastrointestinal track, and shows marked inter individual variation. PHT is known to concentrate in the brain, at levels 5–10 times that found free in the serum. The drug is extensively metabolized in the liver by microsomal enzymes, with the major

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metabolite (50 – 5% of the PHT dose) being 5 – (p-hydroxyphenyl) – 5 – phenylhydantoin (p-HPPH).[7]

In this article a case of Phenytoin-induced gingival hyperplasia is reported with relevant review of literature.

2. Case report

A 17-year-old female patient reported with a complaint of "swollen gums in lower jaw" progressively increasing and causing difficulty in speech & mastication. Past medical history revealed history of seizures for last 1 year, for which she was receiving Phenytoin sodium 100 mg daily.

Patient noticed gradual increase in size in gingivae in mandibular anterior region 3–4 months after Phenytoin administration, which was associated with no pain. Initially she reported to have noticed painless and bead like overgrowth in interdental gingiva between the mandibular incisors which slowly involved the marginal gingiva. Later, she noticed the enlargement in the other teeth gradually causing esthetic disfigurement. It was also causing difficulty in mastication, speech and in maintaining good oral hygiene. The patient had not received any prior dental treatment.

Intra oral examination revealed diffuse gingival overgrowth with pale pink colored margins, papillae and attached gingivae in mandibular arch (1st premolar to 1st premolar region). Margins were firm, dense fibrotic in consistency with rolled out and lobulated contour. Interdental Papillae were bulbous in nature. Diffuse gingival enlargement covering almost 2/3rd of clinical crown height buccally as well as lingually was seen. Oral hygiene was fair with minimum amount of local deposits and without any signs of exudation (Fig. 1). There was lack of true periodontal pockets and presence of coronal increase in size of gingiva suggesting the presence of Pseudo pockets, which were ranging from 4 mm–7 mm (Fig. 2). On examination of teeth, there was Angle's class I molar relation with anterior deep bite and absence of any malocclusion. The patient was otherwise free from any kind of distress or anxiety. Patient was also having anterior deep bite with Angle's Class I molar relationship. The clinical picture and the history procured from the patient were suggestive of drug-induced gingival enlargement.

Treatment began with an Initial phase therapy of thorough oral prophylaxis (Scaling and Root Planing) & oral hygiene instructions. Patient was referred to her physician intimating



Fig. 1 – Displaying gingival enlargement in mandibular arch.



Fig. 2 – Showing 7 mm deep pseudo pockets in mandibular anterior teeth.

him about the gingival enlargement caused due to intake of Phenytoin and to opine whether an alternate drug or dosage of the same drug could be altered. The patient was advised lower dose of Phenytoin i.e. 50 mg daily by her physician to minimize the side effects due to a high dose of Phenytoin. Subsequently, the gingival overgrowths were surgically excised by External Bevel Gingivectomy as suggested by *Zentler* using a scalloped incision. After adequate Local Anesthesia using Lignocaine with 1:80,000 adrenaline, bleeding points were produced at several location points around each tooth in the area using Krane Kaplan Pocket Marker. The series of bleeding points produced described the depth of the pocket in the area scheduled for treatment and was used as a guideline for the incision (Fig. 3). B. P. blade no 15 was used for external bevel incision and to produce a thin and properly festooned margins of the remaining gingiva. The beveled incision was placed at a level apical to base of the pocket in order to establish a "physiologic" contour of the gingival margin. Incision was carried out in lingual as well as buccal direction. After primary incision, secondary interdental incision was carried out and incised tissues were carefully removed using Gracey curette. Remaining tissue tabs and granulation tissues were removed using curette. The exposed tooth surfaces were carefully scaled to remove remnants of calculus deposits and the

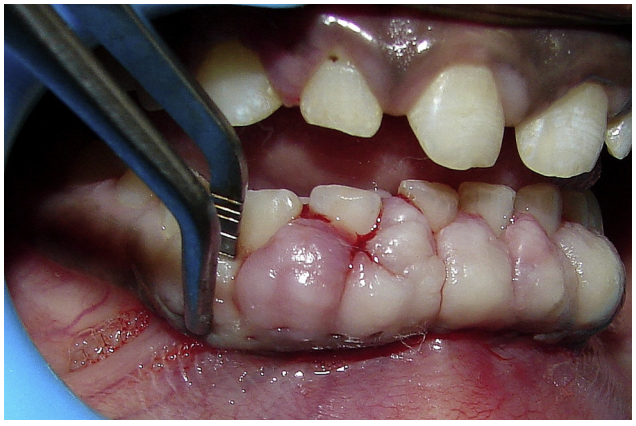


Fig. 3 – Bleeding points produced using Krane Kaplan Pocket Marker.

surgical area was flushed with normal saline (Fig. 4). To protect incised area during the healing, wound surface was covered with a Periodontal dressing (Coe Pack) and the excised tissue was sent for histopathological examination (Fig. 5). Post-operative care included analgesic/antibiotic medications and strict oral care. Patient was also prescribed Chlorhexidine mouth rinse 0.2% twice daily for 15 days. She was recalled after 7 days for removal of periodontal dressing following which she was scheduled to visit after 15 days, 1 month, 3 months, 6 month and 1 year to monitor gingival status and oral hygiene maintenance post operatively.

Microscopic picture of the gingival biopsy specimens revealed connective tissue hyperplasia, acanthosis of overlying epithelium, hyperkeratinised and slightly proliferated stratified squamous epithelium and elongated rete ridges together with few sparse inflammatory cells. Deeper connective tissue showed severe connective tissue infiltrates with some nerve bundles and blood vessels. Connective tissue stroma showed preponderance of fibroblasts. The lesion was diagnosed as fibroepithelial hyperplasia. Based on clinical and histological evidences, it was suggestive of Phenytoin-induced gingival hyperplasia (Fig. 6).

The patient was compliant in maintaining a good oral hygiene. With a follow up period of 6 months and reduced maintenance dose of Phenytoin (50 mg), results were stable and patient did not show any recurrence of enlargement (Figs 7 & 8).

3. Discussion

Anticonvulsants are considered as potential etiologic agents of drug-induced gingival overgrowth[8] although the prevalence of Phenytoin-induced gingival hyperplasia vary from 13 to 50%, in community based studies on institutionalized patients.[9] The pathogenesis of gingival overgrowth is uncertain and not all patients taking anticonvulsants develop overgrowth.[10] Several factors may influence the relationship between the drugs and gingival overgrowth. Those factors include age, genetic predisposition, pharmacokinetic variables, poor oral hygiene, periodontal disease, periodontal pocket depth, gingival inflammation, degree of dental plaque, duration and dose of a drug, histopathology, ultra structural factors, inflammatory changes and drug action on growth factors.[2] A marked heterogeneity of response of gingival fibroblasts to Phenytoin has also been reported.

The underlying mechanism behind drug-induced gingival hyperplasia may also involve inflammatory and non-inflammatory pathways. The proposed non inflammatory mechanisms include defective collagenase activity due to decreased uptake of folic acid, blockage of aldosterone synthesis in



Fig. 5 – Post-gingivectomy photograph.



Fig. 4 – Sectioned gingival tissue.

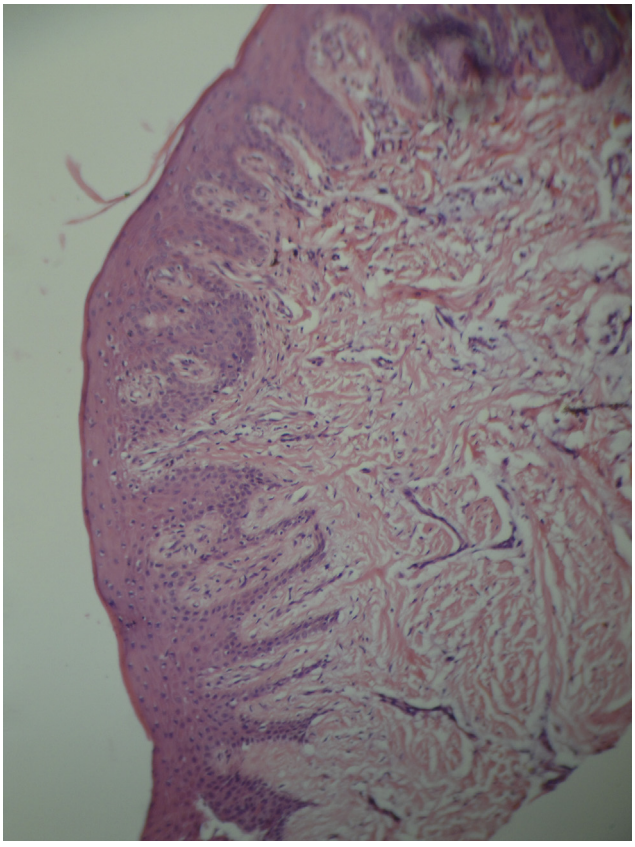


Fig. 6 – Histopathological picture of the sectioned tissue showing keratinized squamous epithelium and dense fibrocollagenous connective tissue with predominance of fibroblasts (H & E, 10 ×).



Fig. 7 – Displaying 15 days post-gingivectomy picture with healed contoured marginal gingivae.



Fig. 8 – Photograph 6 months after gingivectomy.

adrenal cortex and consequent feedback increase in ACTH level and upregulation of keratinocyte growth factor. Alternatively, inflammation may develop as a result of direct toxic effects of concentrated drug in crevicular gingival fluid and/or bacterial plaques. This inflammation could lead to the upregulation of several cytokine factors such as TGF-β1 (Transforming growth factor).[11] Plaque induced gingival inflammation may be an important risk factor in the development and expression of the gingival changes.[12]

In the present case, chronic inflammation in the gingiva of mandibular anterior teeth due to persistent irritation on account of anterior deep over bite can also be a contributing factor in aggravating gingival overgrowth. Drug withdrawal resulted in improvement which is the first step for management of drug-induced overgrowth. Even several alternatives to Phenytoin are available, but they may not be as well tolerated or they may not control seizures effectively. So in the present case, physician advised 50 mg of Phenytoin as compared to 100 mg daily.

The gingival overgrowth could occur with Phenytoin even after 6–7 months of drug administration. Hence the possibility of Phenytoin-induced overgrowth should be considered as early as a possible during its administration to the patient either as an early or late presentation.

Individual author's contribution

Dr. Antush Mittal = Primary Researcher.
Dr. Shoyab Khan = Secondary Researcher.

Conflicts of interest

All authors have none to declare.

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