Management of Phenytoin-Induced Gingival Enlargement: A Case Report

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Gingival enlargement is frequently observed in patients taking certain drugs such as anticonvulsants, immune suppressants, and calcium channel blockers. The effects of these drugs are not only directed at the primary target tissues, but also on secondary target tissues, such as gingival connective tissue, causing clinical, and histopathological aberrations. These aberrations can adversely affect speech, mastication, tooth eruption, and esthetics. Disfiguring gingival overgrowth triggered by these medications often impairs the nutrition and provides access to oral infection, caries, and periodontal disease. The present case report describes the treatment of a patient with a phenytoin induced gingival enlargement.

Keywords: Anticonvulsants, Calcium channel blockers, Connective tissue, Esthetics, Gingival overgrowth, Immunosuppressive agents, Phenytoin

INTRODUCTION

Gingival enlargement or gingival overgrowth are the current terms for all medication-related gingival lesions, previously known as gingival hyperplasia or gingival hypertrophy. The first drug-induced gingival enlargements reported were those produced by phenytoin (Dilantin). Dilantin is a hydantoin, introduced by Merritt and Putnam in 1938 for the treatment of all forms of epilepsy, except the petit mal.¹ Soon after its introduction, published reports were linking the drug with gingival enlargement.² Other hydantoins known to induce gingival enlargement are ethotoin and mephentoin. Other anticonvulsants that can cause gingival enlargement are succinimides and valproic acid.³ Gingival enlargement occurs in about 50% of patients receiving phenytoin, although different authors have reported incidences from 3% to 84.5%.²,⁴⁻⁶ Vigabatrin is a relatively new antiepileptic agent that has been proven to cause gingival overgrowth.⁷

Calcium channel blockers are drugs developed for the treatment of cardiovascular conditions such as hypertension, angina pectoris, coronary artery spasms, and cardiac arrhythmias. They inhibit calcium ion influx across the cell membrane of the heart and smooth muscle cells, blocking intracellular mobilization of calcium. This induces a direct dilation of the coronary arteries and arterioles, improving oxygen supply to the heart muscle. It also reduces hypertension by dilating the peripheral vasculature. Calcium channel blockers include dihydropyridine derivatives (amlodipine, felodipine, nicardipine, nifedipine), benzothiazine derivatives (diltiazem), and phenylalkylamine derivatives (verapamil).³ Nifedipine is one of the most commonly used antihypertensive drugs, and 20% of patients taking this drug report gingival enlargement.⁸⁻⁹ There are reports of large gingival overgrowths in kidney transplant recipients who take nifedipine combined with the immunosuppressant cyclosporine A (CsA).¹⁰ The calcium channel blockers diltiazem, felodipine, nitrendipine, and verapamil also induce gingival enlargement.¹¹ The dihydropyridine derivative isradipine is reported not to induce gingival overgrowth, and can replace nifedipine in some cases.¹² CsA is a powerful immunosuppressant, widely used for prevention of transplant rejection as well as for management of a number of autoimmune conditions, such as rheumatoid arthritis.¹³ Successful use of CsA in transplant medicine has been limited by the development of prominent renal, cardiac, and gingival fibrosis.¹⁴⁻¹⁵ Gingival lesions were reported in the first clinical trials of this medication.¹⁶ Clinical manifestations of gingival enlargement frequently
appear within 1-3 months after initiation of treatment with the associated medications. Clinical and microscopic features of gingival enlargements caused by different drugs are similar.

**CASE REPORT**

A 40-year-old male patient reported to the outpatient department of periodontology and oral implantology, RUHS-CODS, Jaipur with a chief complaint of generalized swollen gums which bleed on slight provocation (for the last 3 years), with 3rd grade mobility in lower anterior teeth leading to an unesthetic smile (Figure 1). He requested treatment which would eventually enhance his smile. His medical history revealed epilepsy since the age of 20, controlled with medication (phenytoin 100 mg BID) for the last 4 years. Gingival tissues were pale pink, enlarged, firm, and fibrotic with pronounced stippling. Generalized bleeding on probing was present. An orthopantomograph of the patient revealed considerable generalized bone loss (Figure 2). Complete hemogram results were under normal limits. A diagnosis of generalized drug-induced gingival enlargement superimposed with periodontitis was made. With the consent of the patient and his physician, complete professional oral prophylaxis was performed, along with a prescription of a 0.2% chlorhexidine mouthwash twice daily for 7 days. The patient was informed about the surgical procedure, and his written consent was obtained for gingival and/or periodontal surgery. After the local anesthetic (2% lignocaine with 1:80,000 adrenaline) was infiltrated in the maxillary anterior region, the initial scalloped internal bevel incision was made with a no. 15 blade, at least 3 mm coronal to the mucogingival junction, and included the creation of new interdental papillae. The same blade was then used to thin the gingival tissues in the buccolingual direction; this thinning process was carried out to the mucogingival junction. At the mucogingival junction level, the blade established contact with the alveolar bone and a full-thickness flap was elevated. The gingival tissue collar that was attached to the bone and teeth was removed with the use of curettes. Following scaling and root planning, flaps were repositioned on top of the alveolar crest, and sutures were placed using an interrupted technique with black braided 3-0 silk sutures. Post-operative instructions were given, and a periodontal dressing was placed for 8 days. Sutures were removed after 8 days. Healing was uneventful. Then surgery was performed in the similar way for the 3rd and 4th quadrant with a periodic interval of 1 week and the lower anterior teeth with 3rd grade mobility (Tooth number: 31, 32, 41, 42) were extracted. Figures 3 and 4 show the operated site at 3 and 9 months recall, respectively.

**Post-operative Care**

The following post-operative instructions were given: For the first 24 h, 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 unoperated side of the mouth. Do not brush over the surgical site. Use chlorhexidine oral rinse (as prescribed) no <24 h after surgery, and do not rinse

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**Figure 1:** Pre scaling views of the patient. (a) Buccal view, (b) right Lateral view, (c) left Lateral view

**Figure 2:** Orthopantomograph showing bone loss

**Figure 3:** (a and b) Postoperative views at 3 months

**Figure 4:** (a and b) Postoperative views at 9 months
vigorously on the 1st day. The patient was prescribed an antibiotic (amoxicillin 500 mg TID for 3 days). For the management of post-operative pain, the patient was also prescribed anti-inflammatory analgesic drugs (ibuprofen 400 mg and paracetamol 325 mg TID after meals for 3 days). In the case of hyperacidity, an antacid (pantoprazole 40 mg before meals BID for 3 days) could be consumed. After 1 week, the sutures were removed. The patient was recalled 1 month, 3 months, and 9 months post-operatively to observe the healing progress.

RESULTS

Healing was uneventful. After periodontal surgeries, there was no post-operative swelling, pain, fever, or any other complication. 3-month follow up revealed no recurrences of gingival enlargement. Patient was satisfied with the esthetic and functional outcome.

DISCUSSION

Phenytoin-induced gingival enlargement occurs most often in younger patients.\textsuperscript{18} Its occurrence and severity is not necessarily related to the dosage after a threshold level has been exceeded.\textsuperscript{7} Tissue culture experiments indicate that phenytoin stimulates proliferation of fibroblast-like cells and epithelium.\textsuperscript{19,20} Fibroblasts from phenytoin induced gingival overgrowth show increased synthesis of sulfated glycosaminoglycans in-vitro.\textsuperscript{21} Phenytoin may induce a decrease in collagen degradation as a result of the production of an inactive fibroblastic collagenase.\textsuperscript{22} Hassell and Page 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.\textsuperscript{23} A genetic predisposition is also a suspected factor in determining whether a person treated with phenytoin will develop gingival enlargement or not. The current understanding is that the pathogenesis of gingival enlargement induced by phenytoin is not known, but some evidence links it to a direct effect on specific, genetically predetermined subpopulations of fibroblasts, inactivation of collagenase, and plaque-induced inflammation.\textsuperscript{24,25}

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.\textsuperscript{26} 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 in the prevention and overall management of gingival enlargement in humans.\textsuperscript{27}

Treatment

Presence of drug-induced gingival enlargement is associated with pseudo-pocket formation. Therefore, the possibility of periodontitis to develop due to plaque accumulation exists. For that reason, meticulous removal of plaque on a frequent basis helps in the maintenance of attachment levels.\textsuperscript{28} The most effective treatment of drug-related gingival enlargement is substitution of medication.\textsuperscript{29} Substitution of the drug should be done in conjunction with the patient’s physician. If any drug substitution is attempted, it is important to allow 6-12 months to elapse between discontinuation of the offending drug and the possible resolution of gingival enlargement before a decision to implement surgical treatment is made.\textsuperscript{30} Professional debridement with scaling and root planing has been shown to offer some relief in gingival overgrowth patients.\textsuperscript{31} Gingival enlargement may persist after drug substitution attempts and good plaque control. These cases need to be treated by periodontal surgery: Either gingivectomy or a periodontal flap.\textsuperscript{26} Consultation with the immunosuppressed patient’s physician regarding antibiotic and steroid coverage should be done prior to any surgical treatment.\textsuperscript{32} Blood pressure and/or any other systemic illness should be controlled prior to the surgery in order to avoid post-operative hemorrhage. The clinician’s decision to choose any of the surgical techniques must be made on a case-by-case basis, and should take into consideration the extent of the area to be treated, the presence of osseous defects combined with the gingival enlargement lesions, and the position of the bases of the pockets in relation to the existing mucogingival junction.

Maintenance

Recurrence of drug-induced gingival enlargement is a reality in surgically treated cases.\textsuperscript{33} Meticulous home care, chlorhexidine gluconate rinses, and professional cleaning can decrease the rate and degree at which recurrence occurs.\textsuperscript{34,35} A hard, natural rubber, fitted bite guard worn at night may also assist in the control of recurrence.\textsuperscript{18} 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.\textsuperscript{26} 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 intraoral sites (maxillary anterior sextant and whole mandibular arch) which did not show improvement by the non-surgical approach were treated by surgical approaches. 3-month follow-up results were positive, with no recurrence of enlargement.

CONCLUSION

Every case of gingival enlargement should be treated in a step-wise manner inclusive of due consultation with patient’s physician, substitution of the drug, non-surgical therapy, and surgical therapy (if needed), followed by supportive periodontal therapy at 3-month intervals.

REFERENCES


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