Management of phenytoin-induced gingival enlargement: a case report

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Gingival enlargements may adversely affect speech, mastication, tooth eruption, and esthetics. These enlargements can occur as a result of the administration of certain anticonvulsants, immunosuppressants, and calcium channel blockers. The present case report describes the treatment of a patient with a phenytoin-induced gingival enlargement. A case of gingival enlargement should be treated in a step-wise manner, including consultation with the patient’s physician, substitution of the drug, nonsurgical therapy, surgical therapy (if needed), and supportive periodontal therapy after every 3 months. In this case, healing was uneventful, and no recurrences occurred 3 months postoperatively.

Key words: drug-induced, phenytoin, gingival enlargement

Gingival enlargement is a well-known consequence of the administration of certain anticonvulsants, immunosuppressants, 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 nutrition, and provides access for oral infection, caries, and periodontal disease.

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 & Putnam in 1938 for the treatment of all forms of epilepsy, except the petit mal. Soon after its introduction, published reports were linking the drug with gingival enlargement. Other hydantoins known to induce gingival enlargement are ethotoin and mephenytoin. Other anticonvulsants that can cause gingival enlargement are succinimides and valproic acid. Gingival enlargement occurs in about 50% of patients receiving phenytoin, although different authors have reported incidences from 3% to 84.5%. Vigabatrin is a relatively new antiepileptic agent that has been proven to cause gingival overgrowth.

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 heart and smooth muscle cells, blocking intracellular mobilization of calcium. This induces 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). Nifedipine is one of the most commonly used antihypertensive drugs, and 20% of patients taking this drug report gingival enlargement. There are reports of large gingival overgrowths in kidney transplant recipients who take nifedipine combined with the immunosuppresant cyclosporine A (CsA). The calcium channel blockers diltiazem, felodipine, nitrendipine, and verapamil also induce gingival enlargement. The dihydropyridine derivative isradipine is reported not to induce gingival overgrowth, and can replace nifedipine in some cases. 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. Successful use of CsA in transplant medicine has been limited by the development of prominent renal, cardiac, and gingival fibroses. Gingival lesions were reported in the first clinical trials of this medication.

Clinical manifestations of gingival enlargement frequently appear within 1 to 3 months after initiation of treatment with the associated medications. Clinical and macroscopic features of gingival enlargements caused by different drugs are similar.

Clinical features

The growth starts as a painless, bead-like enlargement of the interdental papilla, and extends to the facial and lingual gingival margins. As the condition progresses, the marginal and papillary enlargements unite; they may then develop into a massive tissue fold covering a considerable portion of the crowns, and they may interfere with occlusion. When uncomplicated by inflammation, the lesion is mulberry shaped, firm, pale pink, and resilient, with a minutely lobulated surface and no bleeding tendency. The enlargement characteristically appears to project from beneath the gingival margin, from which it is separated by a linear groove. The presence of the enlargement makes plaque control difficult, often resulting in a secondary inflammatory process that complicates the gingival overgrowth caused by the drug. The resultant enlargement thus becomes a combination of the increase in size caused by the drug and the complicating inflammation caused by bacteria. Secondary inflammatory changes not only add to the size of the lesion caused by the drug, but also produce a red or bluish red discoloration, obliterating the lobulated surface demarcations and increasing the tendency to bleed. Enlargement does not occur in edentulous areas. The enlargement...
is chronic, and slowly increases in size. When surgically removed, it can recur. Recurrence may occur as early as 3 to 6 months after surgical treatment. Residual local irritation and systemic or hereditary conditions causing non-inflammatory gingival hyperplasia are the responsible factors. Spontaneous disappearance of enlargement occurs within a few months after discontinuation of the drug.2,20

**Histopathology**

Drug-induced gingival enlargement consists of a pronounced hyperplasia of the connective tissue and epithelium. There is acanthosis of the epithelium and elongated rete-peggs extending deep into the connective tissue, which exhibits densely arranged collagen bundles, along with an increase in new blood vessels and fibroblasts. An abundance of amorphous ground substance has also been reported.21

**Risk factors**

**Poor plaque control**

The severity of gingival enlargement in patients taking these medications correlates well with poor plaque control and is commensurate with the degree of plaque-induced inflammation.22,23 The importance of plaque as a cofactor in the etiology of drug-associated gingival enlargement has been recognized in the most recent classification system for periodontal diseases.24 In this classification, *drug-induced gingival enlargements* are categorized as plaque-induced gingival diseases modified by medications.

Other factors affecting the occurrence of gingival enlargement may include gender—with males being 3 times as likely to develop overgrowth—and age, which is inversely correlated.22,23 Most studies on daily phenytoin, CsA, or nifedipine have not reported a significant association between dosage and the severity of enlargement.25-27 Examination of tissue typing data in transplant recipients has shown that HLA B37-positive patients are significantly more likely to show severe gingival enlargement, whereas the opposite is true for HLA DR1-positive patients.28 Interactions between simultaneously administered medications affecting gingival enlargement have also been reported. Chronic co-medication with phenytoin and other anticonvulsant agents does not affect the degree of gingival enlargement in adult epileptic patients.29 However, CsA-treated patients are often co-medicated with prednisolone or azathioprine, which can decrease the severity of gingival enlargement.30 In contrast, patients on CsA who are also receiving a calcium channel blocker present with a greater severity of gingival enlargement than patients medicated with CsA alone.31 The choice of calcium channel blocker used in conjunction with CsA 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 CsA and amlodipine is higher than those receiving CsA and nifedipine.32 In addition, when the effects of a combined treatment of CsA and nifedipine or diltiazem were tested in an animal model, CsA was found to synergistically enhance gingival growth with nifedipine, and to a lesser degree, with diltiazem.33

**Pathogenesis**

**Role of fibroblasts**

Fibroblasts from overgrown gingiva in phenytoin-treated patients are characterized by elevated levels of protein synthesis, most of which is collagen. Susceptibility or resistance to pharmacologically-induced gingival enlargement may be governed
by the existence of differing proportions of fibroblast subsets (which exhibit a fibrogenic response to these medications) among individual patients.34

Role of inflammatory cytokines
A synergistic enhancement of collagenous protein synthesis by human gingival fibroblasts was found when these cells were simultaneously exposed to nifedipine and interleukin-1β (IL-1β), a pro-inflammatory cytokine that is elevated in inflamed gingival tissues.35 In addition to IL-1β, IL-6 may play a role in the fibrogenic responses of the gingival tissues to these medications.36 IL-6 appears to target connective tissue cells such as fibroblasts both by enhancing proliferation and by exerting a positive regulation on collagen and glycosaminoglycan synthesis.37,38 Therefore, this cytokine has been proposed to play a pathogenetic role in fibrotic diseases, such as pulmonary and gingival fibroses.39

Role of matrix metalloproteinase synthesis and function
Because most types of pharmacological agents implicated in gingival enlargement have negative effects on calcium ion influx across cell membranes, such agents may interfere with the synthesis and function of collagenases.40 Human gingival fibroblasts treated with clinically relevant CsA doses exhibit significantly reduced levels of matrix metalloproteinase (MMP-1 and MMP-3) secretion; these reduced levels may contribute to the accumulation of extracellular matrix components.41

This report documents a case of diffuse drug-induced gingival enlargement treated by different periodontal therapies including non-surgical and surgical approaches in different areas of the mouth.

Case report
A 30-year-old female patient reported to the outpatient department with a chief complaint of generalized swollen gums which bled on slight provocation (for the last 2 years), leading to an unesthetic smile (Fig. 1). She requested treatment which would eventually enhance her smile. Her 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 bone loss in the lower posterior regions (Fig. 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 her physician, complete professional oral prophylaxis was performed, along with a prescription of a 0.2% chlorhexidine mouthwash (10 ml BID for 7 days). After 1 week, the gingival condition improved and the patient was asked to maintain oral hygiene with a soft, gentle toothbrush and warm saline gargles (Fig. 3). She was also asked to discontinue the chlorhexidine mouthrinse. With the patient’s and physician’s consent, phenytoin was substituted with gabapentin (300 mg TID after titration of the dose). Patient was recalled for supportive periodontal therapy after 1 month, 3 months, and 6 months. Substantial enlargement of gingival tissues was present at the 6-month recall visit (Fig. 4). Consultation with the patient’s physician revealed that this patient had no systemic history that would contraindicate the surgical procedure under local anesthesia. The patient was informed about the surgical procedure, and her written consent was obtained for gingival and/or periodontal surgery. Approximately 4-4.5 ml of local anesthetic (2% lignocaine with 1:80,000 adrenaline) was infiltrated in the maxillary anterior region under strictly aseptic conditions. 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 planing, flaps were repositioned on top of the alveolar crest, and sutures were placed using an interrupted technique with black braided 3-0 silk sutures.

Postoperative instructions were given, and a periodontal dressing was placed for 8 days. Sutures were removed after 8 days. Healing was uneventful (Fig. 5).

Following the administration of local anesthesia, a gingivectomy was performed for the lower anterior sextant. First, the deepest point in each pocket (radicular and interproximal surfaces) was marked using a periodontal probe in the pocket and a straight probe on the external gingival wall. The series of bleeding points obtained with the pocket marking served as a guideline for the initial scalloped external bevel incision. This incision was accomplished with a No. 15 blade. A sulcular incision followed the initial external bevel incision and the release of the interproximal tissue was achieved with an Orban knife. Following excision of most of the enlarged tissue with curettes, gingivoplasty was performed with surgical scissors (Fig. 6). Meticulous scaling and root planing was performed before an application of periodontal dressing to the surgical area. Follow-up after 8 days showed uneventful healing. (Fig. 7).
Mandibular left and right posterior regions were treated by modified Widman flaps at different sittings, with a gap of 8 days between the 2 periodontal surgeries (Fig. 8-10). Tissue samples were sent for biopsy. Histopathological examination revealed gingival hyperplasia with inflammatory cell infiltrate and predominance of fibrotic component (Fig. 11).

**Postoperative care**

The surgical wounds were covered with a non-eugenol periodontal pack (Coe-Pak, GC America, Inc.). The following postoperative instructions were given: for the first 24 hours, 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 periodontal pack. Use chlorhexidine oral rinse (as prescribed) no less than 24 hours after surgery, and do not rinse vigorously on the first day. Contact the clinician if the periodontal pack fractures, or if uncontrollable postoperative bleeding and/or unbearable pain occurs. The patient was prescribed an antibiotic (amoxicillin 500 mg TID for 3 days). For management of postoperative pain, the patient was also prescribed anti-inflammatory analgesic drugs (ibuprofen 400 mg and paracetamol 325 mg TID after meals for 3 days). In case of hyperacidity, an antacid (pantoprazole 40 mg before meals BID for 3 days) could be consumed.

After 1 week, the sutures and periodontal pack were removed, and the surgical wound was examined. The patient was recalled 1 month and 3 months postoperatively to observe the healing progress.

**Results**

Healing was uneventful, with all types of periodontal therapies in this patient. After periodontal surgeries, there was no postoperative swelling, pain, fever, or any other complication. Three-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. Its occurrence and severity is not necessarily related to the dosage after a threshold level has been exceeded. Tissue culture experiments indicate that phenytoin stimulates proliferation of fibroblast-like cells and epithelium. Fibroblasts from phenytoin-induced gingival overgrowth show increased synthesis of sulfated glycosaminoglycans in vitro. Phenytoin may induce a decrease in collagen degradation as a result of the production of an inactive fibroblastic collagenase. Hassell & 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. 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.
Gingival enlargement does not occur in all patients receiving phenytoin; when it does occur, there are 3 types:

- **Type I:** Non-inflammatory hyperplasia. Substitution of phenytoin with another anti-epileptic drug is the only method of eliminating this hyperplasia. Subsequent to substitution, the enlargement disappears after a few months.

- **Type II:** Chronic inflammatory enlargement not related to phenytoin use. This enlargement is caused entirely by local irritants, and resembles inflammatory enlargement in patients not receiving phenytoin.

- **Type III:** Combined enlargement. This is a combination of hyperplasia caused by phenytoin and inflammation by local irritation.

**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. 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.

**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.

The most effective treatment of drug-related gingival enlargement is substitution of medication. 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. Unfortunately, not all patients respond to this mode of treatment, especially those with longstanding gingival lesions. The following are possible drug substitutions for the drugs discussed in this article: phenytoin – lomotrigine, gabapentin, sodium valproate, and toprimate; nifedipine – diltiazem, verapamil, and isradipine; CsA – tacrolimus (FK506).

Professional debridement with scaling and root planing has been shown to offer some relief in gingival overgrowth patients. In chronically immunosuppressed patients, papillary lesions present on the surface of the enlarged gingiva have been reported to resolve using topical antifungal medications (such as nystatin lozenges). Slight to moderate gingival enlargement following CsA treatment has been treated with a short course of azithromycin (3 to 5 days, 250 to 500 mg/day), a semisynthetic macrolide derived from erythromycin, that does not affect CsA blood levels. 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. Consultation with the immuno-suppressed patient’s physician regarding antibiotic and steroid coverage should be done prior to any surgical treatment. Blood pressure and/or any other systemic illness should be controlled prior to the surgery in order to avoid postoperative hemorrhage. Sudden unnecessary changes in dental chair position should also be avoided to prevent postural hypotension.

Gingivectomy presents with the advantages of technique simplicity and quickness but, unlike the periodontal flap, will not allow for osseous recontouring, and may sacrifice keratinized tissue. Gingivectomy also results in healing by secondary intention, which causes discomfort and an increased chance of postoperative bleeding. 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. As a general rule, small areas (<6 teeth) presenting with drug-induced gingival enlargement (where there is no evidence of attachment loss and therefore no anticipated need to perform osseous surgery) can be effectively treated with gingivectomy. However, it is recommended that at least 3 mm of keratinized tissue in the apico-coronal direction should remain after the surgical procedure is concluded, so if the initial gingivectomy incision needs to be placed in close proximity to or at the mucogingival junction, this technique is contraindicated.

There is a basic gingivectomy technique used in the treatment of drug-induced gingival enlargement. Following administration of local anesthesia, the deepest point in each pocket (radicular and interproximal surfaces) is marked on the external gingival wall using a pocket marker or a probe. The series of bleeding points obtained with pocket marking works as a guideline for the initial scalloped external bevel incision. This incision is accomplished with the Kirandall knife or a No. 15 blade. A sublacial incision follows the initial external bevel incision, and the release of the interproximal tissue can be achieved with an Orbain knife. Following excision of most of the enlarged tissue with curettes, gingivoplasty is performed with surgical scissors, tissue nippers, and/or high-speed diamonds of various shapes and sizes under adequate coolant. Meticulous scaling and root planing should be performed before application of periodontal dressing to the surgical area. A gingivectomy/gingivoplasty can also be performed by electrosurgery or a laser device.

Larger areas of gingival enlargement (>6 teeth), or areas where attachment loss combined with osseous defects is present, should be treated with a periodontal flap. The periodontal flap technique utilized for the treatment of drug-induced gingival enlargement is a simple variation of the one used for pocket reduction employed to treat periodontitis. Following administration of local anesthesia, sounding of the underlying alveolar bone is performed with a periodontal probe to determine the presence and extent of osseous defects. The initial scalloped internal bevel incision is made with a No. 15 blade at least 3 mm coronal to the mucogingival junction.
including the creation of new interdental papillae. The same blade is then used to thin the gingival tissues in the buccolingual direction; this thinning process should be carried out to the mucogingival junction. At the mucogingival junction level, the blade establishes contact with the alveolar bone and a full or split thickness flap is elevated. The gingival tissue collar, which is attached to the bone and teeth, is removed with the use of large and small curettes. Following scaling and root planing and osseous recontouring when necessary, flaps are positioned right on top of the alveolar crest and sutures are placed using an interrupted or continuous technique with absorbable or nonabsorbable materials. Internal bevel gingivectomy (ledge and wedge technique) has also been suggested as an alternative surgical treatment for gingival enlargements. For this procedure, a gingivectomy incision is placed at a 90° angle to the tooth surface. After removal of the excised tissue, the remaining gingival hyperplastic tissue is thinned, followed by undermining the tissue to remove the fibrotic component. A thin connective tissue layer should remain underlying the epithelium. Then the tissue tabs are removed, and tooth surfaces are scaled and root-planed. The underlying bone is exposed to ensure complete removal of hyperplasia. The flap is then returned to its original position, sutured and covered with a periodontal pack. The use of carbon dioxide lasers has also shown some utility for reducing gingival enlargement, an approach which provides rapid postoperative hemostasis.

Maintenance

Recurrent of drug-induced gingival enlargement is a reality in surgically treated cases. Meticulous home care, chlorhexidine gluconate rinses, and professional cleaning can decrease the rate and degree at which recurrence occurs.

A hard, natural rubber, fitted bite guard worn at night may also assist in the control of recurrence. 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.

Our case was treated first with a nonsurgical 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 introral sites (maxillary anterior sextant and whole mandibular arch) which did not show improvement by the nonsurgical approach were treated by surgical approaches. Three-month follow-up results were positive, with no recurrence of enlargement. Results were appreciated by both the patient and her relatives.

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.

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