CASE REPORT

Phenytoin- and amlodipine-induced gingival overgrowth

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KEYWORDS
amlodipine; drug-induced gingival overgrowth; gingivectomy; phenytoin

Abstract Drug-induced gingival overgrowth is an adverse event associated with three types of drugs, i.e., anticonvulsants, immunosuppressants, and calcium-channel blockers. It was shown that the combined use of an immunosuppressant (cyclosporine) and a calcium-channel blocker increases the prevalence and severity of gingival overgrowth. However, few reports discussed the effects of the combination of an anticonvulsant (phenytoin) and a calcium-channel blocker (amlodipine). In this case report, we present an epilepsy patient who was using both phenytoin and amlodipine, which caused extensive gingival overgrowth. After periodontal treatment and a gingivectomy, the gingival overgrowth was significantly reduced. A postoperative drug-substitution regimen and intensive professional care ensured a stable result 1 year after surgery.

Introduction

Gingival overgrowth is associated with multiple factors including inflammation, adverse events, systemic disease, and neoplastic enlargement. Drug-induced gingival overgrowth is a common consequence of the administration of some anticonvulsants, immunosuppressants, and calcium-channel blockers. Although the pathology of drug-induced gingival overgrowth is not definitively known, these disorders seem to be induced through disruption of homeostasis of collagen synthesis and degradation of gingival connective tissues.

It was shown that the combined use of cyclosporine and a calcium-channel blocker (CCB) increased the prevalence
and severity of gingival overgrowth compared with monotherapy using cyclosporine or the CCB alone.\(^2\)–\(^5\) However, few reports mentioned the gingival status in those receiving a combination of phenytoin and a CCB. This article presents a case of probable synergism with the combined use of phenytoin and a CCB that caused extensive gingival overgrowth in a patient with epilepsy.

**Case report**

A woman 67 years of age presented at the Department of Dentistry in the Hsin-Chu Hospital in Taiwan, with a complaint of gum swelling around the entire dentition. The patient’s medical history disclosed epilepsy for more than 10 years due to left-brain trauma in a traffic accident. She had taken phenytoin since that time. The patient had a stroke attack 1 year before and subsequently took amlodipine in addition to phenytoin.

A clinical examination showed generalized gingival enlargement. The enlarged tissue covered from one-half to two-thirds of the crowns (Fig. 1). Excessive spacing of the anterior teeth was also noted. Probing depths of gingival pockets were at least 5 mm. The patient had compromised oral hygiene. Generalized plaque accumulation and gingival inflammation were evident. A radiographic examination of the posterior teeth revealed 20%–50% bone loss. There were subgingival caries around Tooth Numbers 27 and 36 (Fig. 2). The diagnosis of this case was drug-induced gingival overgrowth with plaque-induced chronic periodontitis.

Following scaling and oral hygiene instructions given to the patient, surgical excision of the overgrowing gingiva under general anesthesia was scheduled because of the patient’s disability and uncooperative behavior. During the surgery, a gingivectomy and gingivoplasty were carried out using surgical knives as well as electrosurgery, which was used to delicately shape the gingival contour without causing active tissue bleeding. In addition, full-mouth scaling and root planing were performed after gingival contouring. After the surgery, the caries lesions of Tooth Numbers 27 and 36 were treated. The gingival contour was much improved. To prevent gingival regrowth, a plaque-control program was begun for the patient. The patient’s physician substituted valproic acid for phenytoin, and captopril [angiotensin-converting enzyme (ACE) inhibitor] for amlodipine. The 1-year postoperative follow-up revealed no recurrence of gingival overgrowth (Fig. 3). The overall gingival inflammation had improved, and the probing depths of the teeth were reduced to 3–4 mm.

The excised tissues were sent for biopsy. Histologic sections showed thickened epithelium and pseudoepitheliomatous hyperplasia (Fig. 4), a large amount of dense bundles of collagen fibers, and mononuclear inflammatory cell infiltration (Fig. 5).

**Discussion**

Drug-induced gingival overgrowth is known to be an adverse effect of three main types of drugs, i.e., phenytoin, an anticonvulsant; cyclosporine, an immunosuppressant; and nifedipine, a CCB, which is widely used to manage cardiovascular disorders. The prevalence rate of drug-induced gingival enlargement was reported to vary: 10%–15% for phenytoin, 8%–70% for cyclosporine, and 0.5%–83% for nifedipine.\(^1\) Gingival tissue reacts differently to various types of medication. As an anticonvulsant, phenytoin has long been used to treat epilepsy, whereas valproic acid is a new antiepileptic and appears to be as effective as phenytoin at controlling seizures. In addition, valproic acid also exhibited a lower occurrence of gingival enlargement.\(^6\)
As an immunosuppressant, cyclosporine was the main choice for organ transplantation in the last two decades. Tacrolimus is a new-generation immunosuppressant and is an excellent alternative to cyclosporine due to its lower incidence of gingival overgrowth and a comparable success rate in organ-graft survival. As a CCB, nifedipine is extensively used to manage hypertension. Amlodipine is a third-generation dihydropyridine calcium antagonist that has similar pharmacodynamic effects as nifedipine. However, amlodipine is characterized by nearly complete absorption and slow hepatic biodegradation. Patients undergoing monotherapy with amlodipine had less gingival overgrowth than those taking nifedipine. A cohort study of 135 renal-transplantation patients demonstrated that the combined use of cyclosporine and nifedipine caused less gingival overgrowth (53%) than that in patients treated with cyclosporine and amlodipine (72%).

Many studies showed that the combined use of CCBs and immunosuppressants enhanced the risk and severity of gingival overgrowth. Spolidorio and colleagues found that the prevalence of gingival overgrowth was 58.3% for cyclosporine use alone and was 84.3% for the combined use of cyclosporine and a CCB. Similarly, Greenberg and colleagues reported that the concomitant use of cyclosporine and a CCB exhibited a higher occurrence of gingival overgrowth (76%) than in those treated with cyclosporine alone (36%). The synergistic effect when using phenytoin and cyclosporine caused severe gingival overgrowth in a kidney-transplant patient. However, few reports mentioned the gingival status related to the combined use of phenytoin and a CCB, which was demonstrated in this article. The pathogenesis of extensive gingival overgrowth following concomitant use of amlodipine and phenytoin in this patient is not clear. Both phenytoin and the CCB inhibit the intracellular uptake of calcium. This synergistic inhibitory action may have affected the secretory properties of gingival fibroblasts or the production of collagenase, subsequently exacerbating the development of gingival enlargement.

The most effective approach to ameliorate gingival overgrowth is withdrawing or substituting medication. In this case, valproic acid and captopril (an ACE inhibitor) were substituted for phenytoin and amlodipine. Gingival hyperplasia associated with valproic acid seems to be extremely rare, and this drug was proposed as an alternative medication in patients with phenytoin-induced gingival hyperplasia. ACE inhibitors are a group of pharmaceuticals that are primarily used to treat hypertension and congestive heart failure. It was suggested that long-term use of an ACE inhibitor may also limit the degree of fibrosis within grafts during chronic cyclosporine usage. To prevent the development of gingival overgrowth, ACE inhibitors may therefore provide greater benefit than CCBs.

Treating the gingival overgrowth lesion itself can be complicated due to the inflammation superimposed on fibrotic tissue enlargement. Several investigations indicated that the severity of gingival overgrowth is directly related to the level of oral hygiene and gingival inflammation. Seymour and colleagues showed that bacterial plaque was a key determinant of the severity of phenytoin-induced gingival overgrowth. It was also demonstrated...
that gingival inflammation is a significant risk factor for phenytoin-6, nifedipine-2, and cyclosporine-associated2 gingival overgrowth. Therefore, a preventive plaque-control program is particularly important for managing drug-induced gingival overgrowth. To achieve excellent plaque control, comprehensive oral hygiene instruction was provided to the patient’s family, and meticulous professional care was delivered to the patient. The 1-year postsurgical follow-up revealed healthy gingiva, and there was no recurrence of gingival overgrowth in the patient.

A case of phenytoin- and amlodipine-induced gingival overgrowth is presented herein. The patient’s normal gingival contour was achieved using a gingivectomy. A post-operative drug-substitution regimen and intensive professional care ensured a stable result.

References


Table 1: Effect of combined drug-induced gingival overgrowth.

<table>
<thead>
<tr>
<th>Combined drug</th>
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CCB = calcium channel blocker; CsA = cyclosporine-A; GO = gingival overgrowth; PH = phenytoin; Tac = tacrolimus.