

# Cilnidipine, a possible instigator for gingival enlargement: A case report

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## ABSTRACT

Calcium channel blockers (CCB's) are commonly prescribed drugs in the management of hypertension. They have been well documented to be associated with gingival overgrowth. The possibility of nifedipine, amlodipine, felodipine, diltiazem and verapamil to cause gingival overgrowth has been elaborated in various case reports. Cilnidipine, a 4<sup>th</sup> generation CCB, approved for treatment of essential hypertension has more advantages compared to conventional calcium-channel blockers and is widely used. In this case report, a chronic kidney disease patient who was under cilnidipine for the management of hypertension presented with features of chronic periodontitis and severe gingival enlargement of 6 months duration. The patient was managed by the change of anti-hypertensive drug and initial periodontal therapy consisting of scaling and root planning. A significant reduction of the gingival overgrowth and inflammation was noticed. It has been 6 months since the implementation of the non-surgical approach, and the patient's periodontal condition has remained stable.

**KEYWORDS:** Drug Induced Gingival Overgrowth(DIGO), Calcium Channel Blockers (CCB), Cilnidipine

## INTRODUCTION

Gingival enlargement is a well known adverse effect of the administration of some anticonvulsants, immunosuppressants and calcium channel blockers. Drug-induced gingival enlargement was first reported in 1939 by Kimball with chronic usage of the antiepileptic drug phenytoin.<sup>1</sup> Gingival overgrowth associated with CCB-nifedipine was first reported in the early 1980s by Lederman et al., Ramon et al., following which, enlargements associated with verapamil, diltiazem, amlodipine and felodipine were also reported.<sup>2</sup> Ikawa et al. presented a case report of severe gingival overgrowth induced by manidipine in a female patient.<sup>3</sup> Irokawa et al. has reported a case of chronic periodontitis with gingival overgrowth in a patient who was under cyclosporine A and cilnidipine following kidney transplantation.<sup>4</sup> Cilnidipine is a novel and unique 1, 4-dihydropyridine derivative calcium antagonist with potent inhibitory action, not only against L-type, but also N-type voltage-dependent calcium channels.<sup>5</sup> It was jointly developed by Fuji Viscera Pharmaceutical Company, Japan and Ajinomoto, Japan and approved for high Blood Pressure(B.P.) treatment in 1995. It has been reported that once daily administration of Cilnidipine resulted in a safe and effective decrease of BP in essential hypertension without excessive reduction or reflex tachycardia than similar administration of other dihydropyridine calcium antagonists.<sup>6</sup> However, it does possess its own set of adverse effects such as nausea, vomiting, abdominal pain, constipation, dry mouth, gingival hypertrophy, peripheral oedema, heartburn, headache, dizziness, light-headedness

and insomnia.<sup>7</sup> There are not much available data in the literature for cilnidipine induced gingival overgrowth. The following report is one such rare case where the enlargement of gingiva manifested clinically within a period of 6 months of cilnidipine administration.

## CASE REPORT

A 45 year old male patient reported to the Department of Periodontics, TNGDC& H with the chief complaint of swollen gums for the past 2 months associated with bleeding while brushing for past 1 month and spontaneous bleeding occasionally. His medical history revealed that he was diagnosed as suffering from chronic kidney disease (stage IV) and hypertension 6 months back. His drug history included cilnidipine 10mg BD, clonidine 0.1mg OD and sodium bicarbonate TDS for the past 6 months. On general physical examination, the patient was moderately built, and vital signs were within the normal range. There were no significant extra oral findings.

Intra-oral examination revealed severe gingival enlargement which was erythematous with lobulated surfaces, rolled out margins and bulbous interdental papilla (Figure1). On palpation, gingiva was soft to boggy in consistency. The enlargement was generalised with more severity in the posterior teeth (Figure2). Poor oral hygiene status of the patient was evident from the presence of local irritating factors contributing to the severe inflammatory component of the gingival enlargement. On probing, the pocket depth was 6-7 mm

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Figure 1: Generalised gingival enlargement with associated inflammation



Figure 3: Two weeks post op after scaling and change of anti hypertensive drug



Figure 2: Figure 2: Pronounced inflammation and enlargement in posterior segments



Figure 4: Post op view after 6 months showing complete resolution of enlargement and inflammation

(generalised) and displayed profuse bleeding. His OPG revealed generalised angular bone loss. The patient was subjected to routine hemogram, and all the parameters were found to be within normal range. Based on the clinical presentation and history of cilnidipine intake, the case was diagnosed as generalised chronic periodontitis associated with cilnidipine induced gingival overgrowth.

During the treatment phase, the patient was first referred to his physician for the opinion regarding change of anti-hypertensive drug following which his medication was changed from cilnidipine to prazosin 5mg. Fitness was obtained from the physician for gingival management under local anaesthesia. Secondly, the patient underwent an initial phase of periodontal therapy involving education and motivation, thorough scaling and oral hygiene instructions. Chlorhexidine oral rinses were prescribed. One week later, root planing was done in two sittings. During the course of treatment, after the change of drug and oral prophylaxis a considerable reduction of enlargement and inflammation was noticed (Figure 3). One month post-operatively there was complete resolution of gingival overgrowth, absence of inflammatory signs and probing depths were reduced to 2- 3mm (generalised). Oral hygiene instructions were reinforced, and patient was kept in maintenance phase. During his follow up visits at 3 months and 6 months post operatively, his gingival and periodontal status remained stable with good oral hygiene maintenance (Figure 4).

## DISCUSSION

The pathogenesis of drug-induced gingival enlargement is still not clear. Factors such as genetic predisposition, age, demographic variables, oral hygiene, pharmacokinetic variables, and molecular and cellular changes in gingival tissues contribute to its multi-factorial aetiology.<sup>8</sup> The most cited causes of gingival overgrowth are increase in the amount of connective tissue matrix dominated by collagen fibres due to the limiting of active collagenase production.<sup>9</sup> Pro-inflammatory cytokines, such as interleukin-1b and interleukin-6 seem to have a synergistic effect in the enhanced collagen synthesis by the gingival fibroblasts.<sup>10</sup> This emphasises the role of the bacterial biofilm in inducing inflammation which leads to production of cytokines and ultimately gingival enlargement.

Drug induced gingival enlargements can be detected clinically as early as 1-3 months following the initial dose of CCB. The enlargement could be restricted to localized areas or appear generalized ranging from mild to severe enlargement of papillary and / or marginal tissues. Initially, it appears as a firm nodular enlargement of the interdental papilla, and in severe cases the gingival tissues have a lobulated appearance due to involvement of entire papillae and surrounding tissues. The overgrown tissue results in the pocket formation, impairs optimal

oral hygiene maintenance and increases susceptibility to oral infection, caries and periodontal disease. The clinical manifestations can range from non-inflamed, firm and fibrous gingiva to one that is oedematous, erythematous and bleeds profusely which is especially seen in patients with poor oral hygiene<sup>11</sup> such as our present case. According to FDA research report on the relationship between cilnidipine and gingival hypertrophy, it was concluded that it could be a possible instigator for the condition with two cases of gingival hypertrophy among 1264 cases reporting with various adverse effects of cilnidipine. The incidence was 0.1582 % in the report with 101 physicians calling it a possible culprit and 1159 physicians claiming its role unlikely.<sup>12</sup> Our present case is a rare incidence of cilnidipine induced gingival hypertrophy with superadded inflammation.

The management of DIGO is most effectively done by cessation of the offending medication and its substitution with a suitable alternative by the physician. Elimination of local factors and regular maintenance of good oral hygiene decrease the severity of the gingival enlargement and improve the overall gingival health. It may take from 1 to 8 weeks for resolution of gingival overgrowth; in our case, it took 4 weeks. In some patients, the non surgical therapy solely could reduce the gingival overgrowth to reasonable levels, and for others, it could make surgical therapy less demanding.<sup>13</sup> According to Camargo et al., if any drug substitution is done, it is important to wait for 6–12 months between discontinuation of the drug and the possible resolution of gingival enlargement before deciding on surgical approach.<sup>14</sup> The various surgical approaches of drug-induced gingival overgrowth are gingivectomy and gingivoplasty with blades or surgical knives, electrosurgery, laser excision and periodontal flap surgery when bone needs to be modified. Our case improved remarkably well with drug substitution and non surgical therapy alone. Both surgical and nonsurgical therapy comprises the risk of recurrence of drug-induced gingival enlargement, especially when cessation of the offending drug was not done or was temporary. Recurrence could occur in 40% of the patients as early as 3–6 months following the surgical intervention<sup>15</sup> with higher risk in patients with poor oral hygiene maintenance.

## CONCLUSION

Cilnidipine is a promising 4th generation CCB for the management of hypertension with a rational pharmacological profile of dual L/N-type Ca channel-blocking action. Its adverse effects are known, but not much light is thrown in its role to cause gingival overgrowth. With the backdrop of the present case report, it could be understood that cilnidipine does rarely cause gingival enlargement and also substantiates the proposed pathogenesis that poor oral hygiene with the offending drug can cause gingival overgrowth. Strict maintenance of oral hygiene, switching over to alternative drugs and surgical management (if required) remain the main stay

of available treatment options. Further research is necessary to clearly describe the pathogenesis of gingival overgrowth at the molecular level and to explore new avenues in drug designing and preventive / therapeutic modalities.

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