

# Nifedipine Induced Gingival Overgrowth – A Detailed Histopathological and Clinical Analysis: A Case Series

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## ABSTRACT

**Introduction:** Nifedipine is the drug used to treat angina pectoris and arrhythmia causing gingival hyperplasia. Withdrawal of nifedipine leads to the regression of overgrowth of gums and enhances the recovery rate.

**Case Presentation:** Two patients treated with nifedipine were referred for assessment and management for their gingival overgrowth.

**Management and Prognosis:** The patients were initiated with phase I therapy and a spectacular change was noticed after three months of drug replacement. There was retrogression in the magnitude of gingival tissue enlargement in both cases, with nominal fibrotic constituent, along with an improvement in the overall periodontal status.

**Conclusion:** Drug induced gingival overgrowth can be treated initially with drug replacement followed by encouraging conscientious plaque controlling methods. Surgical intercession is undertaken if the overgrowth does not retrogress after drug replacement.

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## INTRODUCTION

Gingival hyperplasia has been reported in patients treated with phenytoin sodium, mephentyoin,<sup>2</sup> valproate sodium,<sup>3</sup> phenobarbital,<sup>4</sup> primidone,<sup>5</sup> and cyclosporine<sup>6</sup>. Nifedipine is the drug used to treat angina pectoris and arrhythmia<sup>7</sup> presented clinical and histopathological gingival hyperplasia associated with the administration of phenytoin sodium.<sup>8</sup> Withdrawal of nifedipine leads to the regression of overgrowth of gums and enhances the recovery rate.<sup>8</sup> This report contains histopathological findings of 2 patients with cardiac disease treated with nifedipine. The possible pathogenesis of gingival overgrowth is discussed.

## CASE PRESENTATION

Two patients treated with nifedipine were referred to the Department of Periodontics, Bapuji Dental College and Hospital, Davanagere, Karnataka, India, for assessment and management of their gingival and dental problems. On intraoral examination both patients revealed nodular enlargement of the gingiva; thus, gingivectomy/diagnostic biopsy was performed.

**CASE 1:** A 46-year-old female patient reported a chief complaint of swelling in the lower front gum for eight months. History revealed that the patient was diagnosed with hypertension five years back and was taking nifedipine (Tab. Adalat 10mg) since then. She noticed the enlargement of her gums in lower anterior region with associated intermittent pain and occasional bleeding.

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On general examination, the patient was moderately built and nourished. Intraoral examination revealed diffuse lobulated/nodular enlargement of gingiva in lower anterior jaw (Grade 2: Millers classification of drug induced gingival enlargement) involving interdental, marginal and attached gingiva. Spontaneous bleeding (Gingival Index-1: Loe and Silness), generalised periodontal pockets 9mm and Plaque

score in the patient was 1.5 (Fair: Silness and Loe). (Figure. 1A and 1B)

The case was provisionally diagnosed as chronic generalised non plaque induced gingivitis according to 2017 world workshop guideline for periodontal and peri implant disease classification, drug induced gingival enlargement in relation to 11 to 17. Patient was advised complete hemogram and all the haematological parameters were found to be within normal range. Upon radiographic examination, Orthopantomogram (OPG) revealed generalized inconsistent bone loss.

**CASE 2:** A 35-year-old male patient reported with chief complaint of bleeding gums while brushing in upper and lower front gum for four months. The medical history showed that the patient was diagnosed with high blood pressure six years ago, and after taking nifedipine (Tab. Adipine 10 mg), he found that the gums of the lower incisors were enlarged, accompanied by repeated pain and intermittent bleeding.

General and intraoral examination revealed patient to be well built and nourished with diffuse lobular/nodular swelling of the maxillary and mandibular gingival tissue (Miller's grade 3 enlargement), involving the interdental, marginal, and attached gingiva. Bleeding on probing seen with Gingival Index score of 3 (Loe and Silness), generalised periodontal pockets seen measuring 8mm and full mouth Plaque score was 1.6 which infers "Fair" (Silness and Loe). (Figure 2A and 2B)

The case was provisionally diagnosed as chronic generalised non plaque induced gingivitis according to 2017 world

workshop guideline for periodontal and peri implant disease classification, drug induced gingival enlargement in relation to 12,13,14, 41, 42, 43, 44, 31, 32, and 33. later Patient was advised complete hemogram and all the haematological parameters were found to be within normal range. Upon radiographic examination, Orthopantomogram (OPG) revealed generalized inconsistent bone loss.

Excisional biopsies were done irt 14 and 15 due to excessive growth of gingival tissue almost covering the crown at palatal aspect in case 01 and 02 respectively, the biopsy samples were then transferred to two different vials containing 10% formalin and sent for histopathological evaluation. Histologic sections of each case, stained with hematoxylin and eosin, were examined by a single pathologist, at the Department of oral and maxillofacial Pathology, Bapuji Dental College and Hospital, Davanagere, Karnataka, India

Histologic features of the gingival biopsies: Biopsies of the patients treated with nifedipine showed a slight to moderate hyperkeratosis, thickening of the spinous layer, fibrosis of the underlying connective tissue with fibroblastic proliferation, and some increase of the number of capillaries with slight chronic perivascular inflammation.<sup>9</sup>

The most striking feature was tubular elongation of the rete pegs consisting of a few layers of basal cells growing almost vertically into the lamina propria. The results were classified according to four grades of hyperplasia based upon the length of the rete pegs (acanthosis):<sup>9</sup> (Figure. 3A,3B,3C and 3D). Case 1 as Grade B Slight hyperplasia, width of epithelium from 0.50



**Fig. 1A:** Maxillary buccal aspect of gingiva



**Fig. 1B:** Maxillary palatal aspect of gingiva



**Fig. 2A:** Maxillary labial aspect of gingiva



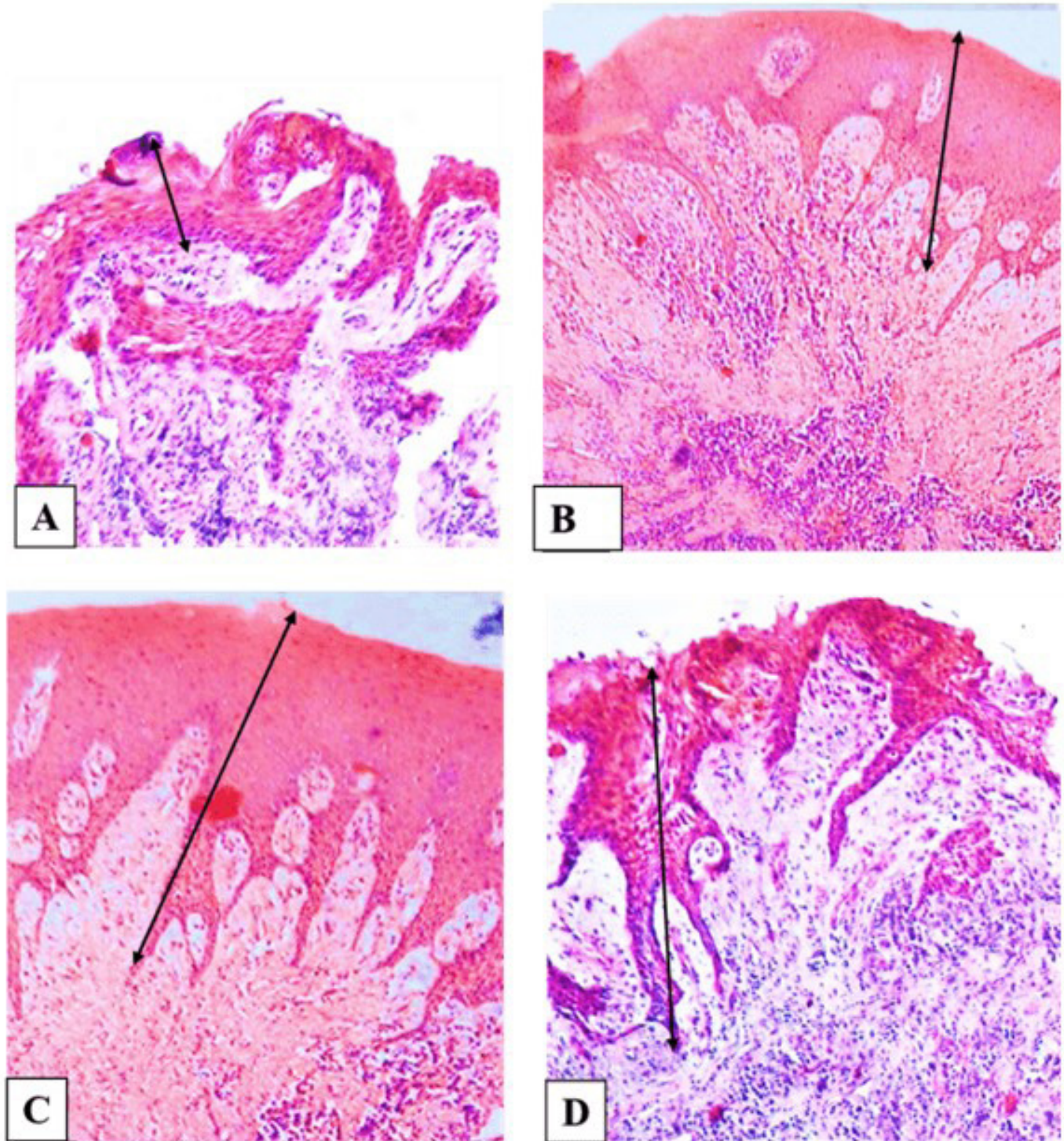
**Fig. 2B:** Maxillary palatal aspect of gingiva



to 1.50 mm (Figure. 4). Case 2 as Grade D Severe hyperplasia, width of epithelium from 3.00 to 4.00 mm (Figure. 5)

Treatment: The patients were initiated with phase I therapy, reckon scaling (Woodpecker Scaler® Gungxi, P. R. China) and

root planing (2R-2L, 4R-4L Columbia, universal currettes Hu-Friedy Mfg. Co., LLC, Tuttlingen, Germany). Subsequently the Patient was referred to cardiologist, apropos drug substitution or withdrawal of the medication. Well ahead the medication



**Figure 3** A. Normal gingivae. Width of epithelium 0.50 mm. Moderate chronic inflammatory infiltration in the lamina propria. B. Gingival hyperplasia with slight acanthosis. Width of epithelium 1.3 mm. The lamina propria shows a slight increase in capillaries with perivascularitis. C. Gingival hyperplasia with moderate acanthosis. Width of epithelium 2.7 mm. D. Marked gingival hyperplasia with production of long rete pegs consisting of several layers of basal cells. Width of epithelium 3.4 mm (Hematoxylin and eosin x 140).

was substituted with Tablet Labetet (100 mg Labetolol, Sun Pharmaceutical Industries Ltd.). Patients were reinforced with OHI (oral hygiene instructions) with the use of Clohex Mouth Wash [Chlorhexidine Gluconate (0.2% w/v), Dr Reddy's Laboratories Ltd.]

A spectacular outcome was noticed after three months of drug replacement and continuation of maintaining a meticulous oral hygiene. There was retrogression in the magnitude of gingival tissue enlargement in both case 01 and 02, with nominal of fibrotic constituent left, along with an improvement in the overall periodontal status by reducing the periodontal pockets to  $\geq 6$  mm from  $\geq 9$  and 8 mm in case 01 and 02 respectively. Hence the full mouth open flap debridement was planned to acquire further pocket reduction via Kirkland's modified flap operation. Postoperatively, there was successful elimination of enlarged gingival tissue and restoration of a physiological gingival contour, complete pocket reduction by having probing depth of 4mm at end of 4 months and 12 months of follow-up period and giving the patient an aesthetically pleasing appearance.

## DISCUSSION

Nifedipine is a very effective Anti-hypertension medication, but long-term usage can cause gingival overgrowth in an enormous part of the populace. In 1984 Lederman et al., testified that the first case of gingival overgrowth affected by the usage of nifedipine.<sup>9,10</sup> Gingival overgrowth instigated by nifedipine, ranged from 14% to 83%, which is far greater than former CCBs (Calcium channel blockers); the prevalence of verapamil and amlodipine are 4.2% and 3.3%, respectively.<sup>9,11</sup> The overgrowth of the gingival tissue caused by CCBs can be seen within the first 3 months of the initial dose, and clinically manifests as localised or generalised gingival overgrowth, affecting the entire dentition.<sup>9-11</sup>

DIGO (Drug induced gingival overgrowth) usually affects the anterior teeth rather than the posterior teeth, and affects the labial/buccal surfaces more than the lingual surfaces.<sup>12</sup> The severe cases extant with widespread engrossment of the interdental papillae, marginal and attached gingival apparatus. In this report, a similar interpretation can be seen in the upper right back tooth region in case 1 and upper right and left back tooth region in case 2. Excessive gingival overgrowth can lead to areas that are difficult to clean with regular brushing. As a result, the host becomes prone to tooth decay, oral infections and loss of alveolar bone. Failure to maintain optimal oral hygiene can lead to inflammation caused by dental plaque, which intensifies gingival overgrowth caused by existing medications. This relationship is important because edentulous areas are least affected by DIGO.

Numerous postulates have suggested for the Etiopathogenesis of gingival overgrowth instigated by CCBs<sup>13-15</sup>. The most intensively studied mechanisms include the effects of matrix metalloproteinases, pro-inflammatory cytokines and fibroblasts:

(1) Since CCB reduces the influx of calcium into cells, the absorption of folic acid is impaired, thereby limiting enzymatic activity of collagenase;<sup>13</sup> Therefore, the breakdown of collagen is reduced, which leads to an increase in collagen deposition.

(2) Another speculative mechanism involves pro-inflammatory cytokines (interleukin-1b and interleukin-6),

which can improve the collagen via enhancement of collagenous protein synthesis by fibroblasts in human gingival tissue.<sup>14</sup>

(3) Since maximum folks compelling CCB have no signs of undue gingival overgrowth; therefore, only a small percentage of fibroblasts can remain sensitive to CCBs. In this sense, the antigens of human lymphocytes may play a pivotal role in the genetic penchant of various phenotypes of gingival fibroblasts to CCBs.<sup>15</sup>

The gingival overgrowth caused by nifedipine is histologically and clinically comparable to phenytoin and cyclosporin-related gingival overgrowth.<sup>9,16</sup> Therefore, the histologically superimposed stratified squamous epithelium is parakeratotic with elongated thin rete pegs. On histological comparison of nifedipine- and diphenylhydantoin-induced gingival overgrowth, attributed that both demonstrated an escalation of extracellular ground substance and fibroblasts.<sup>16</sup>

Still there is a paucity in the literature regarding the correlation between the histological grading of DIGO and its clinical relevance, in the present case series there was a striking clinical and histological relevance in both case 1 and 2. in means of millers clinical grading of 2 and 3, histological grading of B and D, in case 1 and 2 respectively, suggestive of that clinical and histological grading exists mutually.

The rate of gingival overgrowth in patients treated with nifedipine was significantly higher than that of amlodipine. Nifedipine and amlodipine are similar in structure; both belongs to dihydropyridines, but unlike pharmacokinetics.

Amlodipine is polarized and transported along the cell membrane through a more complex transport mechanism, while nifedipine is more lipophilic and therefore easily penetrates the cell membrane. This indicates that the underlying drug-cell interaction mechanism determines the pathogenesis of DIGO.<sup>9</sup>

The difference in half-life and distribution of amlodipine (34 h and 21 l/kg) and nifedipine (7.5 h and 0.78 l/kg) may also affect the predictability of gingival overgrowth after use.<sup>9</sup> These values indicate that most amlodipine is tissue-bound and therefore inactive and not easily available in the blood. It is recommended to determine a certain threshold plasma level from it, Extreme gingival overgrowth began.<sup>17</sup> In contrast to amlodipine, nifedipine tends to reach a significant maximum plasma level, which may trigger DIGO.<sup>18,19</sup>

Substitution of drugs play a vital role in the successful management of gingival overgrowth. All options should be discussed with the patient's cardiologist.<sup>9,18</sup> Non surgical periodontal therapy combined with drug replacements can occasionally lead to a satisfactory reduction in gingival inflammation and helps to improvise the overall periodontal status, which can only be monitored with meticulous oral hygiene maintenance via strict hygiene home care routine and regular dental visits.<sup>9</sup>

Surgical methods are needed to reduce the pockets, remove granulation tissue, restore the topography of the alveolar bone. The main surgical techniques include Open flap debridement. If the drug that causes the DIGO is not stopped/ substituted or treatment is not considered, recurrence of gingival overgrowth may occur.<sup>18,19</sup>

## CONCLUSION

CCBs have been effectively used to treat various cardiac diseases including hypertension, but the serious side effects





is often overlooked. DIGO can be treated initially with drug replacement followed by encouraging conscientious plaque controlling methods. Surgical intercession is scheduled only if the overgrowth does not retrogress after drug replacement and nonsurgical periodontal therapy. Thus, DIGO can be efficaciously succeeded with the above-cited management procedure.

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