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Gingival enlargement improvement following medication change from amlodipine to benidipine and periodontal therapy

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SUMMARY

The use of calcium channel blockers (CCBs) is associated with gingival enlargement, which adversely affects oral function, hygiene and aesthetics. Although CCB-induced gingival enlargement is a known adverse effect, it is rarely or never caused by some CCBs. In this paper, we report the case of a late 80's female patient with hypertension who experienced amlodipine-induced gingival enlargement. The patient's antihypertensive medication was changed from amlodipine to another CCB of the same class, benidipine, which has not been reported to cause gingival enlargement. The patient also received periodontal therapy. A significant improvement in gingival enlargement was noted, and blood pressure control was maintained. This case indicates that it might be beneficial for patients with hypertension presenting CCB-induced gingival enlargement to switch from the CCB that caused gingival enlargement to another CCB with little to no risk.

BACKGROUND

Hypertension is the leading preventable risk factor for premature death and disability worldwide.[1] In 2010, only 36.9% of the global population with hypertension was reported to be receiving appropriate treatment, with just 13.8% achieving blood pressure control.[1] Accordingly, the number of adults with hypertension is expected to increase by approximately 60% by 2025, leading to a total of 1.56 billion people with the condition[2]; in Japan, the number of hypertension cases will reach approximately 43 million.[3] Although the rates of treatment and control of hypertension have increased, the control rates are barely 40% and 45% for men and women, respectively.[3] The need for antihypertensive drugs is increasing not only in Japan, but worldwide, and as more people are prescribed antihypertensive drugs, adverse effects such as gingival hyperplasia may increase.

One of the most frequently prescribed types of antihypertensive drugs is calcium channel blockers (CCBs), which are classified into three categories: dihydropyridine derivatives, phenylalkylamine derivatives and benzothiazepine derivatives. Drug-induced gingival enlargement, which deteriorates oral cleaning, aesthetics and oral function, is a well-known adverse drug reaction associated with some antiepileptics, immunosuppressants, high-dose oral contraceptives and CCBs.[4]

CCBs that have been reported to induce gingival enlargement include nifedipine, nitrendipine, felodipine, amlodipine, nicardipine, manidipine, nisoldipine, cilnidipine, diltiazem and verapamil.[5–11] The reported incidence of gingival enlargement varies depending on the pharmacological agent used (table 1). Although this adverse effect of CCBs has been widely reported, some CCBs have rarely or never been reported to cause gingival enlargement.

In this paper, we report a case of an elderly female with hypertension who was treated for periodontal disease after switching her medication from amlodipine to benidipine, a CCB of the same type, and whose amlodipine-induced gingival enlargement was improved and maintained.

CASE PRESENTATION

A late 80's woman visited our clinic in February 2017 with chief complaints of gum bleeding and denture incompatibility. The patient had been diagnosed with hypertension at the age of 77 and had begun antihypertensive therapy with amlodipine (5 mg/day). Two clinical blood pressure measurements were taken at the first visit, which were 154/83 and 137/74 mm Hg. The patient did not have a history of smoking.

Gingival enlargement, which the patient was unaware of, was observed in the mandibular anterior teeth gingiva and maxillary edentulous areas at the first visit (figure 1). Periodontal examination (54-site measurements of nine teeth) was performed, including probing pocket depth (PPD), which involves measuring the depth of the spaces between the teeth and gingiva as indicative of periodontitis progression; bleeding on probing (BOP), which detects inflammation in the periodontal pocket; sites of suppuration and O'Leary's plaque control record (PCR) to examine oral hygiene.

At baseline, the results of the periodontal examination showed an average PPD of 7.3 mm. The PPD of 98.1% of the sites was 4 mm or more, and BOP was observed in 100% of the sites. The patient routinely performed oral hygiene using only a toothbrush for 1 min after breakfast and before sleeping. Abundant plaque accumulation (PCR, 100%), inflammation of the periodontal tissues and calculus were observed at the first visit. The vertical dimension of the lower face was reduced due to incompatible dentures and pathological tooth migration caused by the periodontitis progression (figure 1). Radiographic examination revealed moderate horizontal alveolar bone resorption, widening of the periodontal ligament of the upper teeth and localised severe vertical alveolar bone

Table 1 List of CCBs with reported association with gingival enlargement

CCBs		Incidence in previous reports (%) (total number of subjects using each drug)					
Class	Pharmacological agent	Jorgensen (1997)[6]	Ellis *et al* (1999)[7]	Ono *et al* (2008)[8]	Kaur *et al* (2010)[9]	Karnik, Bhat and Bhat (2012)[10]	Blocking activity of CCBs
Dihydropyridine	Nifedipine	–	6.3 (442)	7.6 (347)	2.9 (448)	–	L-type
Dihydropyridine	Nitrendipine*	–	–	–	–	–	L-type
Dihydropyridine	Felodipine	–	–	–	3.2 (31)	–	L-type
Dihydropyridine	Amlodipine	3.3 (150)	1.7 (181)	1.1 (267)	1.7 (706)	5.1 (157)	L-type
Dihydropyridine	Nicardipine	–	–	0.5 (219)	–	–	L-type
Dihydropyridine	Manidipine	–	–	1.8 (111)	–	–	L-type
Dihydropyridine	Nisoldipine	–	–	1.1 (89)	–	–	L-type
Dihydropyridine	Cilnidipine*	–	–	–	–	–	L-/N-type
Benzothiazepine	Diltiazem	–	2.2 (186)	4.1 (196)	3.2 (252)	–	L-type
Phenylalkylamine	Verapamil	–	–	–	2.0 (197)	–	L-type

Five studies that report the incidence of calcium channel blocker-induced gingival enlargement are summarised in this table.[6–10] The previous studies indicate that CCBs that activate only L-type calcium channels tend to cause gingival enlargements.

*Nitrendipine and cilnidipine have been reported to cause gingival enlargement; however, to the best of our knowledge, there are no reports on the incidence.[5 11]

CCBs, calcium channel blockers; L-type, long lasting type; N-type, neural type.

resorption on the mandibular right premolar and molar. Based on these clinical findings, severe generalised chronic periodontitis (stage IV grade B, classification in 2018)[12] and drug-induced gingival enlargement[4] were diagnosed.

TREATMENT

At the beginning of the initial treatment, we presented a list of CCBs that were previously reported to cause gingival enlargement and their incidence (table 1) to her physician to determine the possibility of replacing amlodipine. After the consultation, amlodipine was replaced with another dihydropyridine CCB (benidipine 8 mg/day), which has not been previously reported to be associated with gingival enlargement. Subsequently, the clinical blood pressure was well controlled at 127/73 mm Hg.

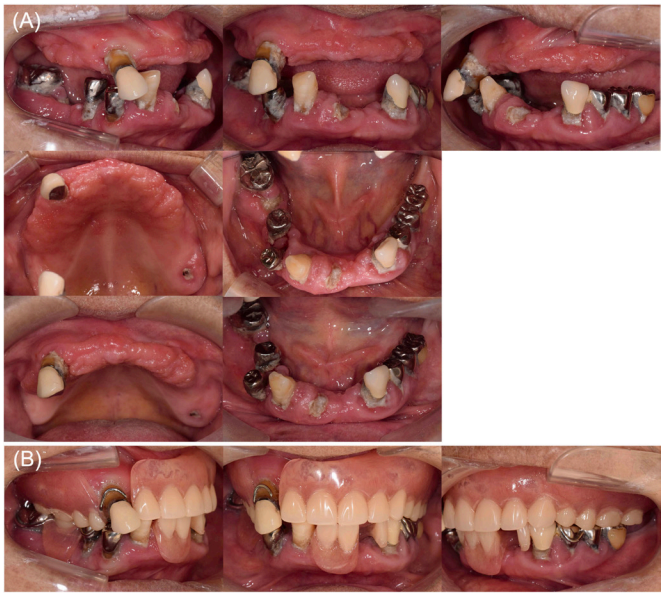

Figure 1 Intraoral photograph at first diagnosis (A, B). (A) Gingival enlargement was observed at the mandibular anterior teeth gingiva and maxillary edentulous areas at the first diagnosis. Abundant plaque accumulation, inflammation of the periodontal tissues, and pathological tooth migration due to periodontitis progression were observed at the time. (B) The vertical dimension of the lower face was reduced due to incompatible dentures.

Initial periodontal therapy included oral hygiene instruction using a toothbrush and an interdental brush, scaling of supragingival calculus and extraction of seven teeth (13, 27, 42, 44, 45, 46 and 47, using the Two-Digit World Dental Federation Notation tooth numbering system) because of the loss of supporting bone and disturbed masticatory function. Then, complete and partial denture fabrication for the upper and lower arches, respectively, and scaling root planing under local anaesthesia were performed. As a result, gingival enlargement improved, and 6 months after replacing amlodipine, an open flap debridement was performed as a preprosthetic procedure at the lower left canine and premolar where PPD of 4 mm or more persisted. Then, prosthodontic treatment with maxillary full dentures and mandibular partial dentures and crowns was performed after re-evaluation at 4 months after the flap operation, and supportive periodontal therapy (regular maintenance) was initiated.

OUTCOME AND FOLLOW-UP

During the initial periodontal treatment, gingival proliferative findings showed a tendency to improve 3 months after amlodipine replacement. Moreover, in the edentulous area of the maxilla, the proliferative findings were reversed 4 months after amlodipine replacement. The clinical parameters at the regular maintenance visit, 14 months after the start of benidipine treatment, remained improvement and were as follows: the average PPD was 2.8 mm, sites with 4 mm or more were 8.3%, and the rate of sites with BOP was 25.0% (figure 2). Furthermore, no recurrence of gingival enlargement was observed for 2 years up to the point that the patient stopped coming to our clinic due to ambulatory issues.

DISCUSSION

CCB-induced gingival enlargement was first reported for nifedipine in 1984,[13] and the first case of amlodipine-induced gingival enlargement was reported in 1993.[14] Other case reports have also associated other CCBs with gingival enlargement.[5–11] According to previously reported cases of CCB-induced gingival enlargement, the prevalence rates associated with amlodipine,

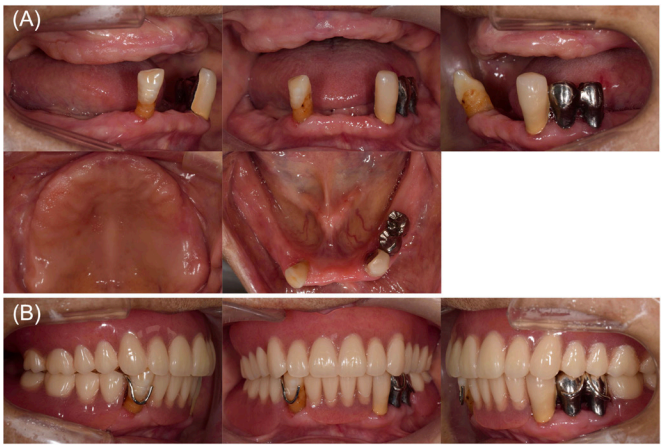

Figure 2 Intraoral photograph after periodontal therapy following the switch from amlodipine to benidipine (A, B). (A) Amlodipine was replaced with benidipine, another dihydropyridine-based calcium channel blocker, which has no reported association with gingival enlargement. A significant improvement was observed in gingival enlargement. (B) Prosthodontic treatment performed with maxillary full dentures and mandibular partial dentures.

nifedipine, felodipine, nicardipine, manidipine, nisoldipine, diltiazem and verapamil were 1.1%–5.1%, 2.9%–7.6%, 3.2%, 0.5%, 1.8%, 1.1%, 2.2%–4.1% and 2.0%, respectively.[6–10] Nitrendipine and cilnidipine have also been reported to cause gingival enlargement,[5 11] but to the best of our knowledge, there are no reports on their incidence. In 2021, a study on the Turkish population reported that 1 of 14 subjects taking benidipine had early mild overgrowth, and 2 of 15 subjects taking lercanidipine presented moderate overgrowth.[15]

Gingival proliferation caused by phenytoin is clearly the most fibrotic, while lesions caused by cyclosporine are highly inflammatory and show little fibrosis.[16] In contrast, lesions caused by nifedipine are of mixed type[16] and might be relatively difficult to diagnose. However, as the Turkish study showed high incidence rates for several drugs, including angiotensin-converting enzyme inhibitors and angiotensin receptor blockers that had not been previously reported, to be associated with gingival overgrowth, grades 1 and 2 of the classification of gingival overgrowth[17] used in this study might include gingival swelling due to gingivitis. In addition, gingival enlargement has not been reported in any CCB other than the above, suggesting that the incidence is rare.

Discontinuation of CCBs or switching to another drug often results in the improvement of gingival enlargement, and thus, drug dosage reduction or discontinuation is the initial treatment approach. However, it may be difficult to replace CCBs that cause gingival enlargement with other antihypertensive drugs in patients with severe hypertension or polypharmacy. Westbrook *et al* evaluated the effect of switching to dihydropyridine derivatives, which are associated with a lower incidence of gingival enlargement, on nifedipine-induced gingival enlargement. Patients with nifedipine-induced gingival enlargement were divided into the following two groups: those receiving continuous nifedipine (six patients) and those receiving nifedipine-equivalent isradipine (five patients), and clinical findings were evaluated after 8 and 12 weeks. Three out of five patients in the isradipine group had clinically reduced gingival enlargement, whereas four out of six patients in the nifedipine group reported increased gingival enlargement.[18]

The mechanisms of pathogenesis of CCB-induced gingival enlargements remain unclear. Calcium (Ca) channels are classified into the following types: the neural type (N-type), which exists in the nerve terminal, the long-lasting type (L-type) characterised by a slow rate of inactivation and the transient type (T-type) characterised by a rapid rate of inactivation.[3] These Ca channel subtypes exhibit various physiological functions due to differences in the electro-physiological properties and mode of in vivo distribution. It is noteworthy that CCBs that act only on L-type Ca channels, such as nifedipine and amlodipine,[3] tend to induce gingival enlargements (table 1). On the contrary, benidipine, which acts on L-/T-/N-type Ca channels, cilnidipine, which acts on L-/N-type Ca channels and azelnidipine, which acts on L-/T-type Ca channels,[3] have rarely or never been reported to cause gingival enlargements. These findings suggest that the subtype and α_1 subunits (Cav1.1, 1.2, 1.3, 1.4, Cav2.1, 2.2, 2.3 and Cav3.1, 3.2, 3.3) of Ca channels[19] on which the CCB acts may be related to the onset and incidence of gingival enlargements. Therefore, we focused on CCBs other than L-type CCBs, which have not yet been reported, and on those with a low incidence of gingival enlargement.

Previously, we reported a case of gingival enlargement in a patient with severe hypertension whose gingival enlargement improved after initial periodontal therapy following a change from L-type CCB (nifedipine, 40 mg/day), which caused gingival enlargement, to L-/T-type CCB (azelnidipine, 16 mg/day), which has not been reported to be associated with gingival enlargement.[20] In the present case, change from a dihydropyridine class L-type CCB (amlodipine), which caused gingival enlargement, to another CCB of the same class L-/R-/T-type CCB (benidipine), for which no association with severe enlargement was reported, along with initial periodontal therapy, significantly improved gingival enlargement. Periodontal variables, particularly dental plaque and gingival inflammation, are also important risk factors for CCB-induced gingival enlargement.[21] Therefore, removal of bacterial factors by initial periodontal therapy, such as oral cleaning, scaling and scaling root planing is effective. Interestingly, even in the edentulous area of the maxilla, which is less susceptible to dental plaque, the gingival enlargement findings disappeared after this drug change. The involvement of lymphocytes expressing delayed rectifier K^+ channels (Kv1.3) has also been demonstrated in the development of chronic inflammatory diseases. It has been reported that benidipine effectively suppresses lymphocytes Kv1.3.[22] Thus, benidipine may contribute to the improvement of inflammation. Therefore, benidipine itself may have contributed to the improvement of inflammation and to the improvement of gingival enlargement in edentulous areas. Future studies are expected in this regard.

Based on these findings, for gingival enlargement caused by CCBs, a change from CCBs to other antihypertensive agents should be considered prior to periodontal treatment. In particular, for those with reduced hand dexterity in oral cleaning and reduced awareness of plaque control (eg, the elderly), changing medications may be a useful option for treating gingival enlargement. In addition, for patients who have difficulty changing from one CCB to another antihypertensive drug, for example, those who have difficulty controlling their blood pressure or those who take multiple drugs, changing to another CCB that is less likely to cause gingival enlargement is recommended. Benidipine could also be a candidate as the CCB after a drug change. Furthermore, oral examination of gingival enlargement and regular dental examinations are recommended for patients taking CCBs. Although improvement was observed in this patient, it is unclear and controversial whether switching CCBs

will improve other cases of CCB-induced gingival enlargement. Therefore, further investigation and case reports about CCB-induced gingival enlargements are needed.

Learning points

- Oral examination of gingival enlargement and regular dental examinations are recommended for patients taking calcium channel blockers (CCBs).
- Most CCBs that have been reported to be associated with gingival enlargement are long lasting-type CCBs.
- It is recommended for patients with CCB-induced gingival enlargement to switch from CCBs to other types of antihypertensive drugs or to a different CCB that has little to low incidence of gingival enlargement prior to periodontal therapy.
- For those with reduced hand dexterity in oral cleaning and reduced awareness of plaque control (eg, the elderly), changing medications may be a useful option for treating gingival enlargement.
- In particular, if it is difficult to change to another CCB, such as for patients who have difficulty controlling their blood pressure or who are taking multiple medications, it may be advisable to change to another CCB of the same class that has not been reported to cause gingival enlargement.

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Case reports provide a valuable learning resource for the scientific community and can indicate areas of interest for future research. They should not be used in isolation to guide treatment choices or public health policy.

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