Case Report

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Amlodipine-induced gingival hyperplasia in a Nepalese patient experiencing high dosages: a case report

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Introduction and importance: Amlodipine is a third-generation calcium channel blocker used in the treatment of hypertension. One of the side effects associated with amlodipine is gingival hyperplasia mostly occurring at a higher dose (10 mg). There are very few cases of gingival hyperplasia associated with amlodipine at a lower dose (5 mg) or short-term administration.

Case presentation: A 51-year-old male patient with diagnosed hypertension sought medical attention for gingival swelling and bleeding from the gums while brushing. He had been under amlodipine 5 mg for 12 months, which was increased to 10 mg for the last 2 months. The history and physical examination were consistent with amlodipine-induced gingival hyperplasia. The first line of treatment consisted of discontinuation of amlodipine and substitution with another class of anti-hypertensive.

Clinical discussion and conclusion: The presented case highlights the challenge of balancing economic considerations with potential side effects in the use of amlodipine for hypertension in low-income countries like Nepal. Given its availability at no cost or minimal expense, amlodipine is often initiated as a first-line therapy. However, the decision to increase the dosage to 10 mg/day, influenced by economic constraints and the drug's affordability, raises the risk of gingival hyperplasia. This case emphasizes the importance of physicians being mindful of potential adverse effects when prescribing higher doses of amlodipine and underscores the need for continued vigilance in managing hypertension in resource-limited settings.

Keywords: amlodipine, case report, gingival hyperplasia, hypertension

Introduction

Calcium channel blockers (CCB) are widely used for the treatment of hypertension and angina pectoris[1]. Amlodipine is preferentially used as a first-line therapy for the management of hypertension in rural areas of Nepal, as it is made available free of charge by the government of Nepal[2]. Pharmacological profile of amlodipine:

- Long-acting dihydropyridine (other members: nifedipine, nicardipine, isoradipine, nitrendipine, and felodipine).
- Mechanism of action: coronary and peripheral arterial vasodilatation.
- Dosage: 2.5 or 5 g, single dose (alone or in combination with atenolol).
- Adverse effects: headaches, facial flushing, dizziness, edema, gingival hyperplasia.
- Oral effects: detectable in gingival crevicular fluid.

HIGHLIGHTS

- Gingival overgrowth is a serious side effect that accompanies the use of amlodipine.
- It is found that amlodipine-induced gingival overgrowth occurs within 2–3 months of onset at a dose of 10 mg/day and rarely within the first 6 months of onset at a lower dose of 5 mg/day.
- The treatment includes strong stress on maintaining good oral hygiene (frequent professional plaque removal if needed), discontinuing the offending agent, and changing the medication class.

- Significant sequestration of the drug in patients exhibiting gingival overgrowth[3].

One of the serious side effects that accompanies the use of amlodipine is gingival overgrowth[4]. Gingival overgrowth may have multiple causes; however, drug consumption is one of the most common causes[4].

The three main classes of drugs inducing gingival overgrowth are anticonvulsants, immunosuppressive agents, and anti-hypertensive agents[4]. The first report regarding gingival overgrowth caused by the administration of amlodipine was published in 1994[5]. There is less data on reports of gingival hyperplasia with amlodipine at a dose of 5 mg, even after taking it for more than 6 months[6]. Subsequently, other authors reported the onset of gingival overgrowth as a side effect in patients who received 10 mg per day of amlodipine within 2 months[7]. Here we report a case of gingival hyperplasia in a hypertensive patient who has been on amlodipine therapy for 14 months.

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This case report has been reported in line with the SCARE criteria[7].

Case presentation

We present a case involving a 51-year-old male from the rural area of Ghorahi, Dang, situated west from Kathmandu, Nepal, who reported experiencing swelling in the upper and lower gums for the past month. The patient also noted gum bleeding during tooth brushing. Initially, the patient observed a growth over the gums, which has progressively enlarged, hindering proper teeth cleaning.

Upon reviewing the patient's history, it was found that he has hypertension and has been taking amlodipine for the past 14 months. The patient initially presented with a systolic blood pressure ranging from 165 to 175 mmHg and a diastolic blood pressure ranging from 100 to 110 mmHg. Initially prescribed amlodipine 5 mg, the patient continued this medication for 12 months. Despite the treatment, his blood pressure remained elevated, with systolic pressure ranging from 155 to 165 mmHg and diastolic pressure from 95 to 105 mmHg. Due to financial constraints, the patient was unable to afford a combination of a calcium channel blocker and angiotensin receptor blocker (amlodipine and losartan, respectively), as recommended. Consequently, the patient was prescribed amlodipine 10 mg, which is provided free of charge by the Government of Nepal. The patient took the medication for 2 months and then presented with the above complaints.

It is important to note that the patient is very poor and faced challenges in seeking regular medical attention. He couldn't go to hospitals, and there was no proper follow-up due to financial constraints. A non-profit organization conducts free medical camps at the place of patient's residence every 6 months, making it difficult to monitor and adjust the patient's medication promptly. As a result, the dose of amlodipine was not increased to 10 mg sooner and was only changed after 1 year.

Additionally, at the 1-year follow-up, a combination of losartan and amlodipine was prescribed, aiming for better blood pressure control. Unfortunately, the patient's financial situation prevented him from affording this combination medication. Consequently, amlodipine 10 mg was prescribed (two tablets each of 5 mg) taking advantage of the free medication provided by the Government of Nepal to ensure continued treatment for hypertension[2].

There was no prior history of trauma or surgical procedures.

The patient did not have comorbidities like diabetes mellitus, or thyroid disorders. He is a non-alcoholic and non-smoker.

On a general examination, the patient was moderately built and nourished.

Intraoral examination revealed gingiva pink and erythematous in color, soft and edematous in consistency, with a thick and rolled-out appearance. No bleeding was present on probing both the arches. The anterior region of the mandibular gingiva exhibited massive fibrotic overgrowth with a pebbly texture. Also, the anterior region of the maxillary gingiva showed growth over the interdental gingiva (Fig. 1). On palpation, the gingiva was firm, non-tender, and leathery in consistency. The enlargement of maxillary gingival tissue partially covers the crown up to the middle third.

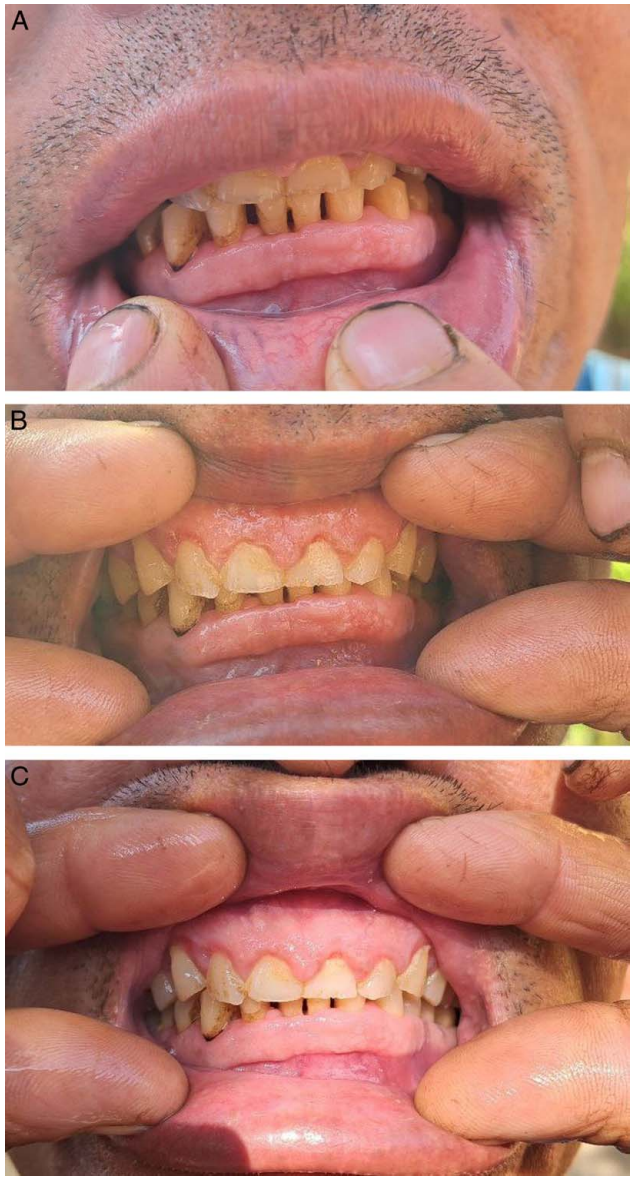

Figure 1. (A-C) Depicting gingival hyperplasia resulting from elevated amlodipine dosage.

Investigations

During the work-up for hypertension, the complete blood count, lipid profile, sugar profile, renal function test, urine routine, and microscopic examination all came out to be in the normal range. (Tables 1–4).

Provisional diagnosis

Gingival hyperplasia secondary to an escalated dose of amlodipine.

Management

Following the identification of amlodipine as the causative factor for gingival hyperplasia, the treatment approach was swiftly adjusted by discontinuing the medication and transitioning to an alternative drug, Losartan 50 mg/day.

Table 1

Showing complete blood count

S.N.	Tests	Results	Units	Reference range
1	Hemoglobin	14.4	mg/dl	12–16
2	Total leukocyte count	7600	cells/microliter	4000–11 000
3	Neutrophils	65	%	50–70%
4	Lymphocytes	33	%	20–40%
5	Monocytes	1	%	1–8%
6	Eosinophils	1	%	0–3%
7	Basophils	0	%	0–2%
8	Platelets	176 000	cells/microliter	150 000–400 000

Unfortunately, the patient could not afford Losartan 50 mg, and the non-profit organization conducting the camps provided the medication free of charge. As the patient was economically disadvantaged, surgical treatment and histopathology were not considered viable options.

The patient could not attend a follow-up appointment due to being located far away, and a follow-up camp at the patient's place of residence is only scheduled for six months later. Therefore, a phone consultation was conducted. During the call, the patient reported a gradual improvement in symptoms, including a noticeable reduction in the size of the gingival hyperplasia.

Discussion

Amlodipine-induced gingival overgrowth has a multifactorial nature, and its appearance and severity are strongly influenced by dosage, duration, and blood level of amlodipine, as well as sex, genetic predisposition (fibroblasts with an abnormal susceptibility to the drug and/or functional fibroblast heterogeneity), oral hygiene status, preexisting gingival inflammation, and activation of growth factors[8]. The underlying mechanism of gingival enlargement remains to be fully understood. However, two main inflammatory and non-inflammatory pathways have already been suggested[9]. The proposed non-inflammatory mechanism includes defective collagenase activity due to decreased uptake of folic acid, blockage of aldosterone synthesis in the adrenal cortex, and consequent feedback increases in the adrenocorticotropic hormone level and upregulation of keratinocyte growth factor. Alternatively, inflammation may develop as a result of the direct toxic effects of concentrated drugs in crevicular gingival fluid and/or bacterial plaques. This inflammation could lead to the upregulation of several cytokine factors, such as transforming growth factor beta 1 [TGF-β1][3].

Table 2

Showing normal lipid profile and HbA1c

S.N.	Tests	Results	Units	Reference range
1	Total cholesterol; serum	118	mg/dl	< 200
2	Triglyceride	132	mg/dl	< 150
3	HDL cholesterol; serum	46	mg/dl	40–60
4	LDL cholesterol; serum	46	mg/dl	< 100
5	VLDL cholesterol; serum	26	mg/dl	< 40
6	Non-HDL cholesterol; serum	72	mg/dl	< 130
7	HbA1c	6.2	%	4.0–6.5

HbA1C, hemoglobin A1C; HDL, high density lipoprotein; LDL, low density lipoprotein; VLDL, very low density lipoprotein.

Table 3

Showing normal renal function test

S.N.	Tests	Results	Units	Reference range
1	Urea	13	mg/dl	7–18
2	Creatinine	0.76	mg/dl	0.50–1.20
3	eGfr	115	ml/min/1.73 m^2	> 90
4	Sodium	144	mmol/l	135–145
5	Potassium	5.2	mmol/l	3.5–5.5

eGFR, estimated glomerular filtration rate.

Furthermore, studies carried out show a modulation of the inflammatory process as the calcium antagonists act as an inhibitor of P-glycoprotein to a variable degree, the genetic product of Multidrug Resistance 1 (MDR1), and inflammation may modify the P-glycoprotein expression, which is expressed in the endothelial layers of blood vessels obtained from healthy or inflamed gingiva. It was also found that gingival pockets or pseudo pockets existed in subjects treated with calcium antagonists (amlodipine) as compared to their drug-free counterparts. It has been found that this drug-related side effect is associated with the MDR1 3435C/T gene polymorphism[10].

In patients with hypertension, the prevalence of gingival overgrowth associated with amlodipine is lower than that associated with other calcium channel-blocking agents, including nifedipine[6]. The majority of the available literature is case stu dies that demonstrate that amlodipine-induced gingival over growth occurs within 2–3 months of onset at a dose of 10 mg/day and rarely within the first 6 months of onset at a lower dose of 5 mg/day[11].

Side effects of amlodipine include constipation, edema, palpitations, dizziness, and flushing, which are more common with the higher dose of 10 mg, as well as, uncommonly, gum hypertrophy with an incidence around 2%[12].

Treatment is generally targeted on drug substitution and effective control of local inflammatory factors such as plaque and calculus[3]. When these measures fail to cause resolution of the enlargement, surgical intervention is recommended. These treat ment modalities, although effective, do not necessarily prevent recurrence of the lesions[3]. The need for, and timing of, any sur gical intervention needs to be carefully assessed. Surgery is nor mally performed for cosmetic/esthetic needs before any func tional consequences are present[3].

In our case scenario, the patient remained free of gingival overgrowth during a year-long course of amlodipine at a daily dose of 5 mg. Nevertheless, upon escalation to 10 mg per day, the patient reported gingival swelling within 2 months of initiating the higher dosage. The treatment includes strong stress on maintaining good oral hygiene (frequent professional plaque removal if needed), discontinuing the offending agent, and changing the medication class. Usually, regression occurs with

Table 4

Showing normal urine routine microscopy

S.N.	Tests	Results	Units	Reference range
1	Protein	Nil	mg/ml	Nil
2	Glucose	Nil	mg/ml	Nil
3	Pus cells	1–2	cells/HPF	1–2
4	RBCs	Nil	Cells/HPF	< 5

RBC, red blood cell.

time[13]. Surgical resection and histopathology were not considered due to patient's financial constraints.

Conclusion

The presented case highlights the significance of amlodipine-induced gingival hyperplasia, particularly when the dosage is increased to 10 mg/day. Amlodipine, readily available at no cost or at a very affordable price, serves as a first-line therapy for hypertension in low-income countries such as Nepal. The decision to escalate the dosage to 10 mg is often influenced by economic considerations, given the medication's accessibility. In resource-constrained settings where financial constraints may limit the prescription of a combination of different anti-hypertensive classes, the free availability of amlodipine becomes a crucial factor in its preferential use.

However, healthcare providers must exercise caution when opting for a higher dose of amlodipine, especially when aiming to achieve better blood pressure control. The observed gingival hyperplasia in this case, following the escalation to 10 mg/day, highlights a potential side effect that physicians should be mindful of when prescribing higher doses of amlodipine.

In low-income settings, where amlodipine is a valuable resource in hypertension management, careful consideration and close monitoring are essential to mitigate adverse effects, such as gingival hyperplasia, and ensure the overall well-being of patients.

Ethical approval

This is a case report; therefore, it did not require ethical approval from ethics committee.

Consent

Written informed consent was obtained from the patient for the publication of this case report and accompanying images. A copy of the written consent is available for review by the editor-in-chief of this journal on request.

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Author contribution

All authors: writing the paper, reviewing and editing, revising it critically for important intellectual content.

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The authors declare no conflicts of interest.

Research registration unique identifying number (UIN)

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Guarantor

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Data sharing is not applicable to this article.

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