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Gingival overgrowth during hypertension therapy. A case report and literature review.

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Abstract

Introduction and purpose: Hypertension is a global public health issue, affecting over 1.4 billion people and is responsible for a significant portion of deaths due to heart disease and strokes. Pharmacotherapy, especially antihypertensive drugs, can lead to undesirable effects, including gingival overgrowth, which is a known drug-dependent phenomenon. Despite the availability of numerous drugs from various pharmaceutical classes, gingival overgrowth still remains a serious health problem, particularly among older patients.

State of knowledge: Drugs such as calcium channel blockers are commonly used in the treatment of hypertension. Amlodipine, a popular calcium channel blocker, is associated with gingival overgrowth, although the incidence of this effect can vary depending on the dose and duration of use. Gingival overgrowth may have multifactorial mechanisms, including drug-cell interactions and the patient's genetic predispositions.

Summary: Drug-induced gingival overgrowth, including amlodipine, is a rare but significant phenomenon that can complicate treatment and lead to serious consequences for the patient. Implementing prophylactic measures, monitoring periodontal state, and continuing periodontal therapy are crucial to minimalize the risk of DIGO. In cases of intensification of symptoms, surgical intervention may be necessary, however, prognosis depends on individual factors, and recurrence can be an issue for susceptible patients.

Keywords: amlodipine, calcium channel blockers, gingival enlargement, gingival overgrowth, gingival hyperplasia

Introduction

Hypertension is becoming an increasing public health challenge, affecting 1.4 billion people worldwide. It is responsible for about half of all deaths related to heart diseases and strokes. (1) Most guidelines recommend the use of angiotensin-converting enzyme inhibitors (ACE-Is) or angiotensin receptor blockers (ARBs), calcium channel blockers (CCBs), and thiazide-like diuretics as first-line drugs in the treatment of hypertension. (2) Some medications used in hypertension therapy can lead to iatrogenic gingival overgrowth. This overgrowth is defined as "an enlargement or overgrowth of the gingiva resulting from systemic drug use" and is known as DIGO (drug-induced gingival overgrowth). (3) Currently, more than 20 drugs from three different pharmacological categories, including anticonvulsants, calcium channel blockers, and immunosuppressants, are associated with gingival enlargement. (4) (Tab.1)

Table.1 Various medications known to predispose to gum enlargement. (5)

Anticonvulsants		*Immunosuppressive drugs*	*Calcium channel blockers*
Phenytoin	*Vigabatrin*	*Cyclosporine*	*Nifedipine*
Ethotoin	*Ethosuximide*	*Tacrolimus*	*Diltiazem*
Mephenytoin	*Topiramate*	*Sirolimus*	*Felodipine*
Phenobarbital	*Pyrimidinone*		*Nitrendipine*
Lamotrigine			*Verapamil*
			Amlodipine

Drug-induced gingival overgrowth (DIGO) typically manifests around the third month after the initiation of pharmacological therapy, more frequently affecting the anterior section of the mandible and maxilla. (6) The shared mechanisms of their action include increased androgen activity in the gingiva, immunosuppressive effects, and the blockage of calcium channels in the cell membrane. (7) In cases of drug-induced gingival overgrowth, the gingival response is dependent on the presence of bacterial plaque. (8) While plaque does not initiate the overgrowth, it affects the severity and extent of the condition. (9) There is a correlation between the degree of gingival overgrowth and the drug dosage, duration of therapy, and the concentration of the drug in the blood and gingival fluid. (10) Calcium channel blockers

inhibit the influx of calcium into cardiac muscle cells and arterial walls, leading to peripheral arterial relaxation and blood pressure reduction (these drugs act on calcium channels, which are electron-charged, located in the plasma membrane). They are used in the treatment of hypertension, arrhythmias, and angina pectoris. (11) Gingival overgrowth occurs in about 20% of patients undergoing therapy with calcium channel blockers. (12) Among these drugs, nifedipine is most commonly associated with gingival overgrowth. (13) Cases involving amlodipine, whose mechanism of action is pharmacodynamically similar to nifedipine, are less frequently reported. (3) The incidence of gingival overgrowth associated with amlodipine is 3.3%, which is significantly lower than that for nifedipine, where it ranges from 14 to 83%. (14) Both drugs are dihydropyridines, thus having a similar structure and being stored in gingival fluid, but they differ in their physicochemical profile. The mechanism of drug-induced gingival overgrowth is complex and multifactorial. The interaction between the drug and the cell plays a crucial role in the pathogenesis of this effect. The physicochemical profile of nifedipine enhances this interaction in gingival tissues, which is not observed to the same extent with amlodipine. (15) Amlodipine has been considered for a long time a safe drug, with a relatively

small number of side effects. However, with increased usage, cases of gingival overgrowth have been reported (16), particularly in patients taking a dose of 10 mg daily. (17) Clinical symptoms of gingival enlargement typically appear one to three months after the start of treatment. (18) The work presents a rare case of gingival overgrowth in a patient with hypertension who has been treated with amlodipine for four months.

Materials and Methods

Clinical case

A 65-year-old man was referred to the Periodontology Clinic due to discomfort related to his gums. The patient reported swelling of the gums mainly in the maxilla, which had been present for about 4 months, although the symptoms were not as intense before. Additionally, he complained of bleeding gums during brushing and eating hard foods for the past 2 months. During the clinical interview, the patient reported suffering from hypertension and regularly taking medication for the mentioned condition: amlodipine (Vilpin 10 mg), bisoprolol (Bicardef 10 mg), Furosemide (40 mg), and Kalipoz 391 mg. During the intraoral examination, generalized nodular enlargement of the gingiva in the anterior maxillary region was observed, along with numerous carious cavities and residual roots. (Fig.1) The altered gingiva overlapped the tooth crowns and partially covered them. On palpation examination, the gingiva was painless, edematous, and bleeding upon probing. The patient exhibited inadequate oral hygiene, evidenced by deposits of supra- and subgingival calculus.

Figure 1. The condition of the patient's gums on the day of their appointment at the Periodontological Clinic.

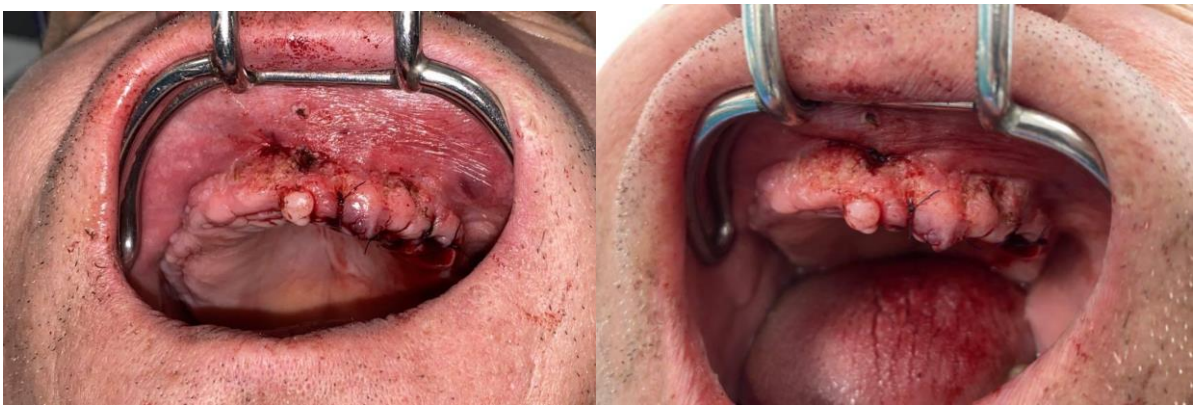
A panoramic radiograph has been made at another dental office, where extractions in the first quadrant were also performed. (Fig. 2) The patient provided radiographic documentation during

the first visit to the periodontal clinic. Radiographic examination revealed horizontal bone loss of grade III and bone pockets adjacent to teeth 15 mesially and 44 bilaterally, with extrusion of tooth 16. Extraction was indicated for the remaining teeth in the maxilla and teeth 38, 44, and 45 in the mandible.

Figure 2. Patient's panoramic radiograph.

The proposed treatment plan included oral cavity sanitation, conservative treatment of tooth 43, and gingival overgrowth correction using a cautery. Subsequently, prosthetic replacement of missing teeth was planned after consultation at the prosthodontic clinic. Discontinuation or replacement of the antihypertensive medications after consultation with the attending physician was not possible. In the first phase of treatment, supragingival and subgingival calculus was removed in SRP protocol, oral hygiene instruction was performed, and the use of 0.2% chlorhexidine mouthwash was recommended for 2 weeks until the next appointment. Two days before the procedure, the patient was prescribed Clindamycin MIP 600 therapy and advised to continue it for 6 days. Using 2% Lidocaine with Noradrenaline for local anesthesia via intra-alveolar injection, tooth extraction was performed in the upper second quadrant. The sockets were sutured with non-absorbable 4/0 sutures. During the same visit, the overgrown gum tissue was also removed using a cautery device. (Fig. 3) Tissue samples were collected for histopathological examination. A follow-up appointment was recommended after 10 days.

Figure 3. The condition of the patient's gums immediately after surgical procedure.



During the follow-up appointment, a reduction in inflammation, decreased swelling of the gums, normal gum architecture, and proper healing of the tooth sockets were observed. (Fig.4) Further appointments were scheduled for the patient to continue treatment according to the previously outlined treatment plan.

Figure 4. The condition of the patient's gums 10 days post-surgical procedure.

The histopathological examination of the excised tissue revealed hyperplastic stratified squamous epithelium with features of parakeratosis, along with connective tissue infiltrated by cells characteristic of chronic inflammation, mainly lymphocytes. The histopathological examination confirmed that the gingival overgrowth is drug-induced.

Literature Review

Scientific literature was searched on PubMed service, in medical literature books, and scientific literature on May 17, 2024, and May 20, 2024. The search covered the years 2014–2024. Keywords such as "gingival hyperplasia" were used, resulting in 538 hits, of which 241 were excluded due to limited accessibility. Additionally, some articles were excluded because they were not relevant to the research topic. Subsequently, after excluding paid-access papers, further searches were conducted using keywords such as "drug-induced gingival hyperplasia," resulting in 28 hits, "drug-induced gum enlargement" with 7 hits, "calcium channel blockers AND gingival hyperplasia" with 28 hits, and "amlodipine AND gingival hyperplasia" with 19 hits. All the mentioned articles were freely accessible. Selected works were mainly in Polish or English; however, this review also included a few articles in other languages, such as German. Additionally, for thorough verification, guidelines from medical literature such as "Contemporary periodontology" by Renata Górska, Tomasz Konopka, "Diagnosis and treatment of diseases of the oral mucosa" by Renata Górska, "Periodontal diseases Classification 2017" by Renata Górska, and "Edra Urban & Partner - Periodontology" by Hans-Peter Mueller. A total of 28 articles formed the basis of this work.

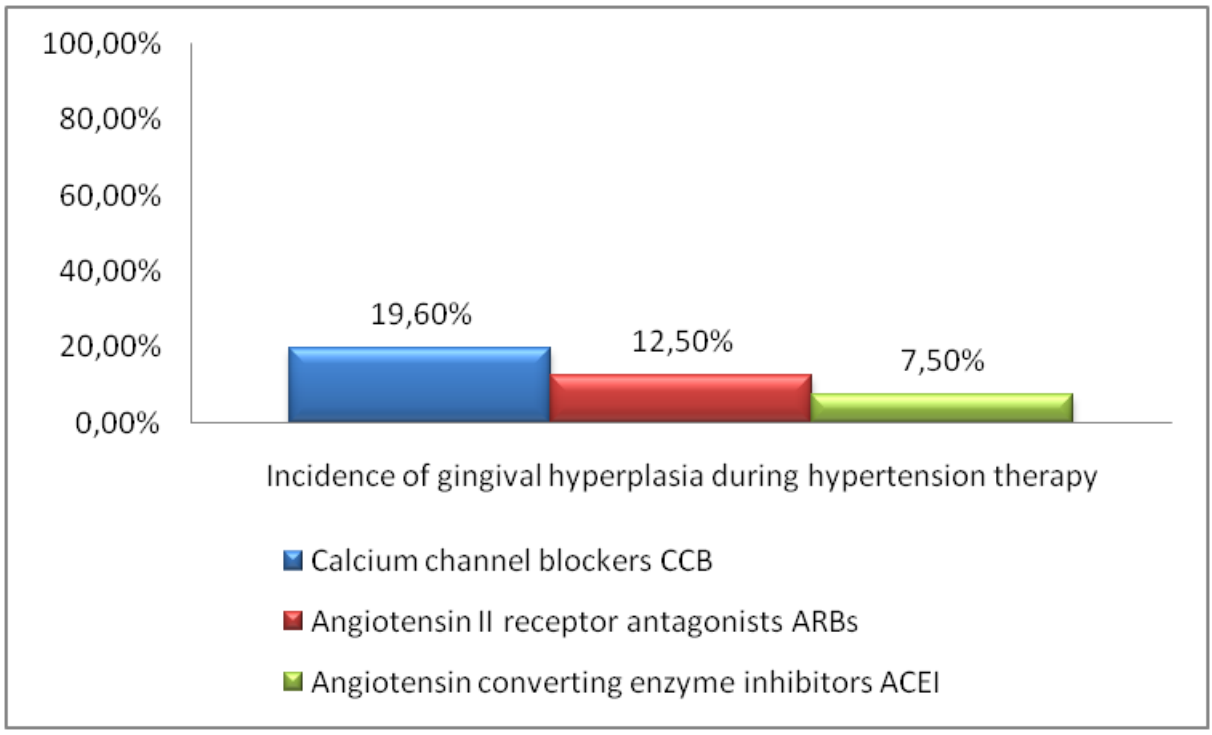
Data Analysis

The clinical case information has been analyzed in the context of the literature review findings. The clinical presentation, treatment methods, and outcomes of drug-induced gingival overgrowth therapy were analyzed. The clinical case served to illustrate both typical characteristics and differences compared to similar cases described in the literature.

Discussion

Hypertension, cardiac arrhythmias, angina pectoris, and coronary artery spasm are cardiovascular conditions that are often prevalent in the population, especially among individuals in middle and older age. Calcium channel blockers are the preferred option in treating these diseases. (19) The incidence of drug-induced gingival overgrowth associated with the treatment of arterial hypertension varies depending on the group of drugs used: CCB, ARB, ACEI. (3) (Diag. 1)

Diagram 1. Incidence of gingival hyperplasia during hypertension therapy.



In a systematic review from 2017, it was established that the most commonly prescribed drug classes for patients with arterial hypertension were CCBs; among available CCBs, amlodipine was the most frequently prescribed medication (37%). (20) A second-generation dihydropyridine calcium channel blocker, known as amlodipine, is associated with gingival overgrowth. (21) Studies indicate that the incidence of amlodipine-induced gingival overgrowth ranges from 1.7% to 3.3% (22) and is similar across various racial and geographic populations and remains stable over time. Men are 3.3 times more likely to develop gingival overgrowth compared to women. (22) Amlodipine is an excellent first-line choice among many antihypertensive drugs. It can be used alone or in combination with other antihypertensive medications. (23) In the treatment of arterial hypertension and angina pectoris in adults, the standard initial dose of amlodipine is typically 5 mg once daily, with the possibility of increasing to a maximum dose of 10 mg per day, depending on the individual patient's response. (24) Gingival overgrowth develops more rapidly and more frequently in patients taking 10 mg of amlodipine daily compared to those taking 5 mg. (25) Gingival overgrowth induced by amlodipine usually appears within the first three months of starting the medication at a dose of 10 mg per day and initially manifests as enlargement of interdental papillae. Amlodipine-

induced gingival overgrowth (AIGO) has a multifactorial nature, and its appearance and severity are influenced by several factors, including the dose, duration of therapy, and concentration of amlodipine in the blood, as well as gender, genetic predispositions, oral administration, and oral hygiene status. (26) Various etiopathogenetic mechanisms of AIGO have been proposed; however, the exact cause remains unclear. Postulated mechanisms include faulty collagenase activity due to decreased folic acid uptake, increased adrenocorticotropic hormone (ACTH) levels due to aldosterone synthesis blockade, elevated levels of keratinocyte growth factor, inflammation due to drug concentration in gingival crevices and bacterial plaques, and increased expression of transforming growth factor-beta. (27) Accumulation of the drug in the gingival crevicular fluid in the presence of bacteria may lead to elevated levels of pro-inflammatory cytokines. (28) The presented clinical case confirms, in line with existing reports, the possibility of gingival overgrowth occurring after the use of amlodipine. However, it is worth noting that this is a relatively rare phenomenon with this particular drug. Due to the necessity of continuing hypertension treatment, discontinuation of amlodipine was not possible. Therefore, the decision was made to perform gingivectomy and remove the upper teeth. This decision was based on information contained in one of the scientific articles, which noted that gingival overgrowth may resolve after tooth extraction and in the case of edentulism. (10) Following the tooth extractions, our patient was already edentulous, suggesting a positive effect of such an approach.

General Clinical and Histological Picture of Drug-Induced Gingival Overgrowth

The starting point of overgrowth is the interdental papilla of the incisor teeth, from where the overgrowth spreads to the marginal gingiva. (12) Uncomplicated overgrowth without inflammation typically progresses painlessly, with non-bleeding gums that appear pale pink, are elastic, firm, and may have a smooth surface or be covered with characteristic stippling. The change in the shape of the gums makes it difficult to maintain proper oral hygiene, chew food, and disturbs occlusion. (29) Failure to treat such a condition leads to disease progression, resulting in destruction of the periodontal tissue and alveolar bone, and ultimately tooth loss. Gingival overgrowth is usually not observed in edentulous areas of the alveolar process. After tooth extraction, gingival overgrowth subsides. (10) The incidence of drug-induced gingival overgrowth varies depending on the type of medication, but the clinical and microscopic appearance of the lesion is similar. (30) Increased proliferation of gingival fibroblasts,

disruption of the balance in collagen synthesis and degradation, increased production of amorphous extracellular matrix, inhibition of apoptosis, and increased number of mast cells are observed. (10) Features of parakeratosis with acanthosis and elongation of epithelial ridges are present. Increased vascularity in the lamina propria, with fibrosis and accompanying infiltration of inflammatory cells, can be observed. (31)

In the differential diagnosis of fibrous overgrowths should be excluded: hormonal disorders, vitamin C deficiency, hematological disorders (leukemia), and neoplastic changes.(10)

Prevention and treatment of gingival overgrowth in patients with DIGO

Preventing drug-induced gingival overgrowth involves regular monitoring of periodontal health, maintaining good oral hygiene, and eliminating local irritants. Establishing a specific oral hygiene plan aimed at reducing plaque buildup, inflammation, and the need for surgical interventions is crucial. For individuals taking medications that can cause gingival overgrowth, systematic periodontal therapy every six months is recommended. (32) Discontinuation or substitution of the medication often leads to spontaneous resolution of the overgrowth. In cases where drug substitution is not possible, such changes are considered non-life-threatening side effects. In some cases, the use of flutamide, a nonsteroidal anti-inflammatory drug with antiandrogenic properties, may be effective in treating medication-induced overgrowth. (10)

For severe overgrowth, surgical intervention may be necessary. The first step should always be hygiene, followed by procedures such as gingivectomy, gingivoplasty, flap surgery, or CO2 laser-assisted surgeries. (19) Before deciding on surgical correction, a 6-12 month observation period after changing medications is recommended. (10) Electrocoagulation may be used in difficult cases, in children, or when the gums are delicate and prone to bleeding. CO2 laser, with its 10600 nm wavelength, is well absorbed by water, making it an effective tool in soft tissue surgery with high water content, such as the gums. (17) Blood vessels up to 0.5 mm in diameter can be effectively closed, providing a dry surgical field, which improves visibility during the procedure. Laser is preferred over a scalpel as it has strong bactericidal and hemostatic properties, further contributing to achieving a relatively dry field and improving visibility during surgery. (18)

Prognosis

The recurrence of drug-induced gingival overgrowth after surgical treatment typically occurs on average between 6 and 12 months in susceptible patients. It is estimated that the recurrence rate reaches 47.2% of cases requiring reoperation. Although laser therapy may be associated with a lower risk of recurrence, conventional and modified methods of traditional gingivectomy remain the gold standard. (3)

Summary

Given the growing problem of drug-induced gingival overgrowth (DIGO) in patients taking amlodipine, this study represents an important contribution to understanding the etiology, prevention, and treatment of this rare but significant complication of antihypertensive pharmacotherapy. Both the clinical case analysis and literature review confirm that gingival overgrowth is multifactorial and may be associated with various drug classes, including amlodipine. Proposed preventive strategies and treatment methods based on establishing oral hygiene protocols, regular monitoring of periodontal status, and considering medication change or surgical intervention may help manage DIGO and improve patients' quality of life. However, further research is necessary to better understand the pathophysiological mechanisms of this phenomenon and to develop more effective therapeutic strategies.

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