Amlodipine-induced Schamberg's Disease: A Case Report

Amani Ibrahim Al Rawahi[1], Haitham Salim Al-Shanfari[2], Haniya Khalfan Al Hasani[1], Ahmed Said Al Salami[3], Nabila Ali Al Julandani[3] and Maisa Hamed Al Kiyumi[4]*

[1]Department of Emergency and Outpatient, Armed Forces Medical Services, Muscat, Oman

[2]Department of Dermatology, Armed Forces Hospital, Muscat, Oman

[3]Department of Hispathology, Armed Forces Hospital, Muscat, Oman

[4]Department of Family Medicine, Sultan Qaboos University Hospital, Muscat, Oman

Received: 16 July 2024

Accepted: 21 August 2024

*Corresponding author: maysa8172@gmail.com

DOI 10.5001/omj.2027.20

Abstract

Schamberg's disease, a benign and progressive form of pigmented purpuric dermatosis (PPD), rarely manifests as an adverse effect of amlodipine therapy. In this report, we present the case of a 46-year-old man with hypertension treated with amlodipine 5 mg and perindopril 5 mg, requiring escalation to 10 mg due to uncontrolled blood pressure. Eleven months later, the patient developed pigmented skin lesions on his shins and ankles, confirmed via skin biopsy as Schamberg's disease. At initial examination, the pigmented lesions were asymptomatic, with no associated itchiness or pain and the blood investigations also revealed normal findings. Upon clinical suspicion of PPD and reviewing the literature and case studies, the association with amlodipine was identified. Thus, amlodipine was discontinued in December 2023, and the patient was transitioned to indapamide 2.5 mg in combination with perindopril 10 mg once daily. At the follow-up appointment (2 weeks later) the skin lesions showed mild improvement with controlled blood pressure and finally, at the six-month follow-up visit, a marked improvement was observed in the lesions. Consequently, it was noted that discontinuation of amlodipine resulted in gradual resolution of the skin rash. All in all, the current findings revealed that amlodipine-induced Schamberg's disease represents a rare adverse event. Hence, physicians should maintain a high level of clinical suspicion for amlodipine-induced Schamberg's disease, especially in patients presenting with purpuric skin lesions following the use of amlodipine, regardless of the duration of use.

Keywords: Amlodipine, Schamberg's Disease, Pigmented Purpuric Dermatosis, Pigmented Skin Lesions, Hypertension.

Introduction

Pigmented Purpuric Dermatosis (PPD) is a rare and chronic skin condition, characterized by pigmented macules and petechial skin lesions of variable sizes, distributed symmetrically over the lower limbs.[1] While the etiology of PPD is not widely known, erythrocyte extravasation and hemosiderin deposition are commonly described as the main attributing cause in histopathology reports.[2] There are five types of PPD: Schamberg's purpura, lichen aureus, Majocchi purpura, eczematoid-like purpura of Doucas and Kapetanakis, and Gougerot-Blum purpura.[2] Schamberg's disease, also known as progressive pigmented purpuric dermatosis (PPD), represents the most prevalent and typically benign form of PPD. It manifests as small reddish puncta resembling cayenne pepper grains, which gradually coalesce to form irregular plaques of orange or brown pigmentation due to hemosiderin deposition. While Schamberg's disease can affect individuals of all ages, it is most commonly observed in patients aged between 8 and 66 years.[2,3] Generally,

patients remain asymptomatic, although itching may occasionally be reported as an associated symptom.[2] Although typically localized to the lower limbs, Schamberg's disease may extend proximally in some cases.[2]

This case report discusses a middle-aged man diagnosed with hypertension and treated with amlodipine, who subsequently developed characteristic skin lesions consistent with Schamberg's disease, as confirmed by biopsy. Notably, cessation of amlodipine therapy resulted in a marked improvement in the skin lesions.

Case Report

A 46-year-old man was diagnosed with primary hypertension in September 2020. Initially, he was prescribed perindopril 5 mg and amlodipine 5 mg once daily. However, due to inadequate blood pressure control, the dose of amlodipine was increased to 10 mg. Eleven months later, the patient developed pigmented skin lesions on both shins, ankles and feet. These lesions were asymptomatic, with no associated itchiness or pain. There was no ankle oedema. Upon examination, irregular, localized, non-blanchable macules and papules were observed, resembling cayenne pepper, and displaying varying shapes and sizes (Figure 1).

Figure 1. Skin lesions compatible with Schamberg´s disease at baseline.

Blood investigations, including full blood count, coagulation profile, early morning cortisol level, vitamin B12, and erythrocyte sedimentation rate (ESR), revealed normal findings.

The patient was referred to a dermatologist who performed a skin biopsy, that revealed a few perivascular lymphocytic infiltrates, scattered dilated blood vessels, and extravasated erythrocytes associated with the presence of hemosiderin deposition that was confirmed by Perls' Prussian blue stain (Figure 2). There is no epidermotropism, vasculitis, or malignancy. These features supported the clinical suspicion of pigmented purpuric dermatosis. Upon reviewing the literature, three case reports were found linking amlodipine to pigmented purpuric dermatosis. Consequently, amlodipine was discontinued in December 2023, and the patient was transitioned to indapamide 2.5 mg in combination with perindopril 10 mg once daily.

The patient returned for a follow-up appointment two weeks later, exhibiting well-controlled blood pressure and mild improvement in the skin lesions. Subsequently, at the six-month follow-up visit, there was marked improvement observed in the skin lesions (Figure 3).

[A]

[B]

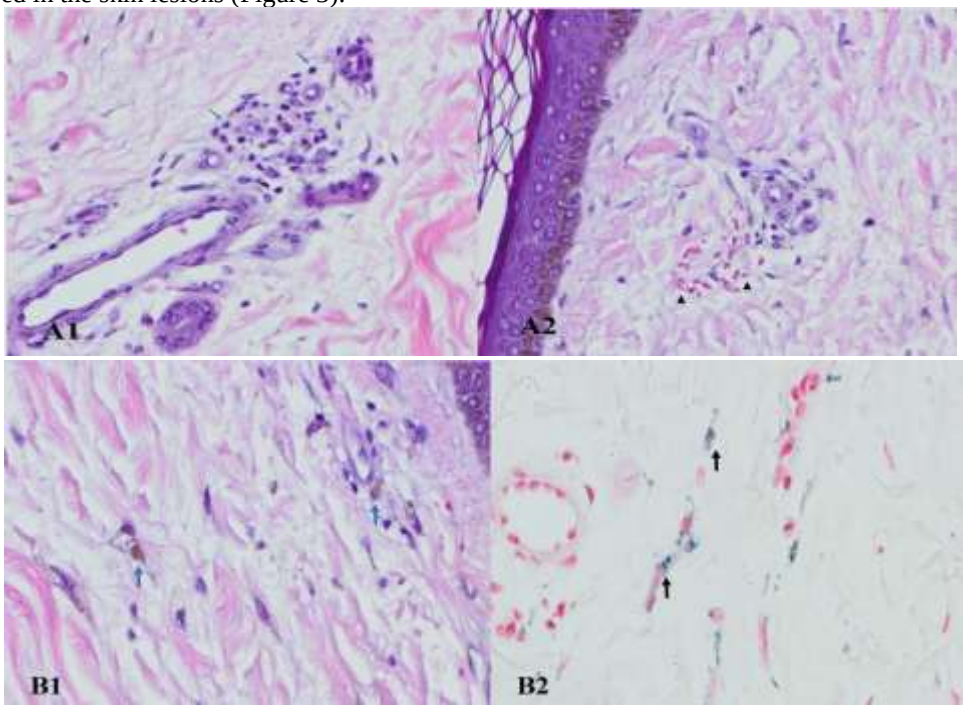

Figure 2. A: Skin biopsy (H&E): mild lymphocytic infiltration (blue arrows) in A1, and red blood cells extravasation (arrowheads) in A2. **B:** Skin biopsy with dermal hemosiderin deposition, brown pigment (blue arrow) in B1, which appears blue in color by Perls Prussian Stain (block arrow) seen in B2.

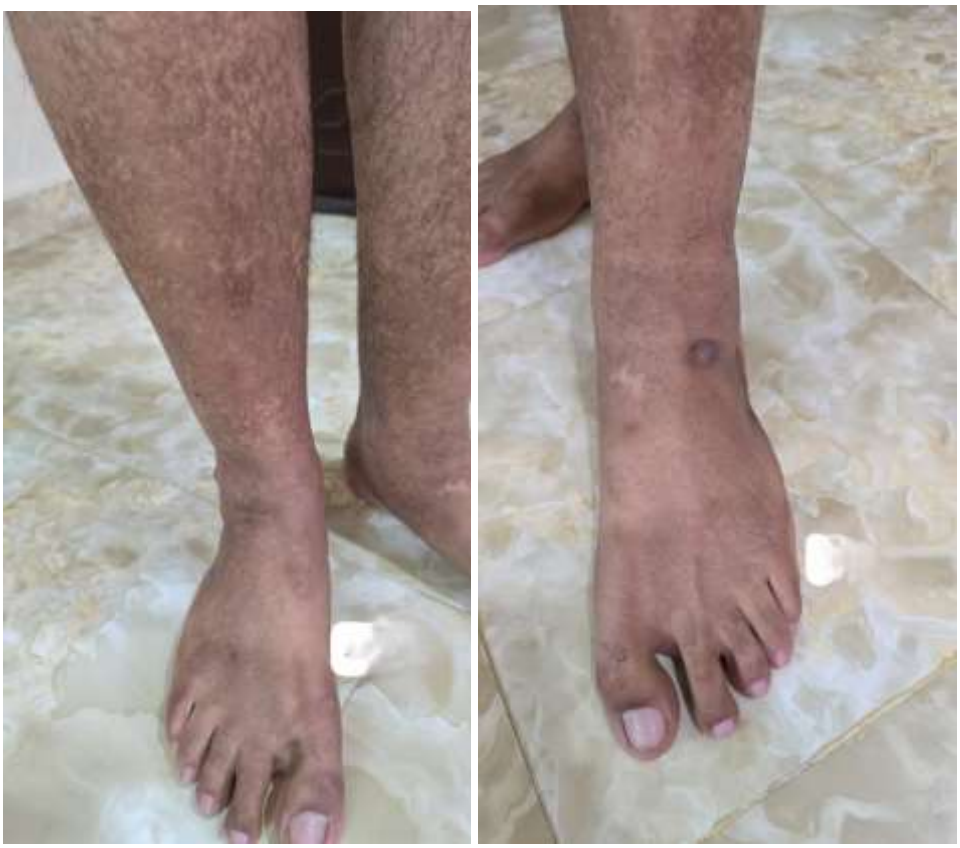

Figure 3. Skin lesions observed six months after discontinuation of amlodipine

Discussion

The current report describes a rare case of progressive pigmented purpuric dermatosis (PPD) induced by amlodipine use. While drugs such as acetaminophen, aspirin, glipizide and nitroglycerin were reported to be linked to the occurrence of Schamberg's disease,[2,4] only three case reports have been published so far linking amlodipine to Schamberg's disease[5-7] (Appendix 1). Amlodipine, an oral dihydropyridine calcium channel blocker, functions by inhibiting voltage-dependent L-type calcium channels, thus impeding the initial calcium influx. Compared to other dihydropyridine calcium channel blockers, amlodipine has the longest half-life (ranging from 30 to 50 hours).[8] Common side effects of amlodipine include peripheral edema, heart failure, pulmonary edema, flushing, and dizziness. Clinical trials have shown a dose-dependent manner of amlodipine side effects. For example, at a dosage of 10 mg, the incidence rates of edema, dizziness, flushing, and palpitations were 10.8%, 3.4%, 2.6%, and 4.5%, respectively.[9]

Schetz and Kocić[5] reported a 31-year-old male with stage 1 hypertension was treated with lisinopril 20 mg daily for 5 weeks, but his blood pressure remained elevated. Amlodipine 10 mg daily was added, resulting in improved blood pressure after 3 months. However, purpuric skin eruptions and ankle edema developed which gradually subsided over four months upon discontinuation of amlodipine. Upon re-initiation of amlodipine, symptoms reappeared, confirming the diagnosis of amlodipine-induced Schamberg's disease based on biopsy findings and causality assessment.

Another case reported by Faria et al.[6] described a 71-year-old woman presented with petechial skin lesions on her lower extremities, evolving over 5 days. Despite chronic medication for hypertension, atrial fibrillation, and dyslipidemia, including dabigatran and amlodipine, there were no recent medication adjustments. Blood tests showed only a slight increase in partial prothrombin time due to dabigatran. She was advised to discontinue dabigatran and omeprazole and start prednisolone and rivaroxaban. However, her lesions worsened over a month, and she was referred

to a dermatologist who diagnosed her as having pigmented purpuric dermatosis (PPD). Topical corticosteroids were prescribed with no improvement. After discovering literature linking amlodipine to PPD, the patient ceased amlodipine, resulting in lesion improvement within a week and complete resolution after a month. At the 6-month follow-up, she remained lesion-free without amlodipine.

While the majority of cases of Schamberg's disease are painless, one case report by Singh et al.[7] presented a severe, progressive and worsening course. In this case report, a 56-year-old man with a history of diabetes, hypertension, and hypothyroidism presented with bilateral leg pain, swelling, and discoloration. His medications included metformin, amlodipine, valsartan, and levothyroxine for many years. Despite various treatments, including ointments, steroids, and antibiotics, the discoloration worsened, and he developed fatigue. Initial work-up revealed acute anemia, elevated inflammatory markers, and positive antibodies. Skin biopsies confirmed pigmented purpuric dermatitis. Discontinuation of amlodipine led to significant improvement upon follow-up and resolution of the skin lesions and even the inflammatory markers.

The pathological mechanisms of this condition remain unknown, but it was likely caused by drug-induced breakdown of erythrocytes outside the capillaries, leading to hemosiderin deposits. This phenomenon has been reported in the literature for other drugs on multiple occasions.[9]

The onset of Schamberg's disease following amlodipine initiation is variable among the published case reports. In two case reports,[6,7] patients were on amlodipine for a long time and then developed skin lesions, whereas in the current case and the case reported by Schetz and Kocić,[5] the Pigmented Purpuric Dermatosis developed shortly upon initiation or incrementation of the amlodipine dose. The explanation for these differences could be attributed to the fact that the side effects of amlodipine are dose-dependent.[10] Also, delayed hypersensitivity to medications is well known and might explain the delayed onset of side effects to amlodipine.[11] All in all, the current case underscores the importance of physicians maintaining vigilance for rare side effects of amlodipine, even with prolonged use.

Conclusion

Amlodipine-induced Schamberg's disease represents a rare adverse event. Physicians should maintain a high level of clinical suspicion for amlodipine-induced Schamberg's disease, especially in patients presenting with purpuric skin lesions following the use of amlodipine, regardless of the duration of use. Given the rarity of this adverse event, it is crucial for healthcare providers to be vigilant and promptly recognize the characteristic skin manifestations associated with this condition. Early identification can prevent unnecessary diagnostic tests and specialist referrals, leading to more efficient management and better patient outcomes. Moreover, raising awareness among healthcare professionals about this potential adverse effect of amlodipine can facilitate timely diagnosis and intervention, ultimately reducing the risk of disease progression and improving patient care.

References

1. Sardana K, Sarkar R, Sehgal VN. Pigmented purpuric dermatoses: an overview. Int J Dermatol 2004 Jul;43(7):482-488.

2. Fujigaki JL, Anjum F. Schamberg Disease. StatPearls Publishing, Treasure Island (FL); 2023.

3. Sharma L, Gupta S. Clinicoepidemiological study of pigmented purpuric dermatoses. Indian Dermatol Online J 2012 Jan;3(1):17-20.

4. Abeck D, Gross GE, Kuwert C, Steinkraus V, Mensing H, Ring J. Acetaminophen-induced progressive pigmentary purpura (Schamberg's disease). J Am Acad Dermatol 1992 Jul;27(1):123-124.

5. Schetz D, Kocić I. A new adverse drug reaction–Schamberg's disease caused by amlodipine administration–a case report. Br J Clin Pharmacol 2015 Dec;80(6):1477-1478.

6. Faria C, Henriques F, Leite J, Fernandes C. Purpura is Not Always Caused by the Anticoagulant. Eur J Case Rep Intern Med 2017 Apr;4(3):000536.

7. Singh G, Jain H, Lamichhane J, Gambhir HS. Amlodipine-Associated Schamberg Disease. Am J Ther 2022 Nov-Dec;29(6):e663-e665.

8. Bulsara KG, Cassagnol M. Amlodipine. StatPearls Publishing, Treasure Island (FL); 2023.

9. Ratnam KV, Su WP, Peters MS. Purpura simplex (inflammatory purpura without vasculitis): a clinicopathologic study of 174 cases. J Am Acad Dermatol 1991 Oct;25(4):642-647.

10. Vukadinović D, Scholz SS, Messerli FH, Weber MA, Williams B, Böhm M, et al. Peripheral edema and headache associated with amlodipine treatment: a meta-analysis of randomized, placebo-controlled trials. J Hypertens 2019 Oct;37(10):2093-2103.

11. Chu M-T, Chang W-C, Pao S-C, Hung S-I. Delayed Drug Hypersensitivity Reactions: Molecular Recognition, Genetic Susceptibility, and Immune Mediators. Biomedicines 2023 Jan;11(1):177.

APPENDIX 1: A summary of previously published case reports of amlodipine-induced Schamberg's disease.

Author and year of publication	Patient's age (years) and gender	Dose of amlodipine and duration of use	Other medications	Treatment received for Schamberg's disease	Time to resolution of skin lesions	Follow-up
Schetz and Kocić (2015)	31 years, Man	10 mg, recent (3 months)	lisinopril 20 mg	Amlodipine was discontinued	3-4 months	Amlodipine was reinitiated again and the skin rash reappeared after 1 month.
Faria et al. (2017)	71 years, Woman	5 mg, chronic use, no recent adjustment in the dose	- Nebivolol 5 mg once a day - Simvastatin 20 mg once a day - Olmesartan 20 mg once a day - Dabigatran 110 mg twice a day - Omeprazole 20 mg once a day.	- Topical corticosteroid - Amlodipine was discontinued	1 month	At 6 months, no recurrence of skin lesions.
Singh et al. (2022)	56 years, Man	- Dose was not mentioned. - Duration: for many years	-Metformin -Valsartan -levothyroxine	- Skin ointments, emollients, topical steroids, and systemic antibiotics - Amlodipine was discontinued	4 weeks (marked improvement)	Not mentioned