CASE REPORT

# Amlodipine-induced Generalised Exfoliative Dermatitis: Not to be Missed!

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**Abstract**

Amlodipine a calcium channel blocker (CCB), is commonly used in treating hypertension, coronary artery disease, and chronic kidney disease. It is considered a first-line treatment for high blood pressure. Amlodipine acts by selectively inhibiting voltage-gated L-type calcium ion channels, which consequently decreases systemic vascular resistance, total vascular resistance, and muscle contractility. We report a case of amlodipine-induced exfoliative dermatitis, highlighting the importance of recognizing this rare but serious cutaneous reaction to amlodipine, a commonly used drug in primary care. Prompt discontinuation of the offending drug and appropriate management are crucial for improving patient outcomes. Clinicians should maintain a high index of suspicion for drug-induced exfoliative dermatitis in patients presenting with generalized erythema and scaling after initiating new medications.

**Keywords**: *Amlodipine, calcium channel blocker, exfoliative dermatitis.*

## Introduction

Exfoliative dermatitis is an uncommon but serious skin disorder that clinicians must be able to recognize [1]. This skin condition is characterized by widespread erythema (redness of the skin) and exfoliation (shedding of the skin).[1] Drug-induced cases are frequently associated with anticonvulsants, and rare occurrences involving specific antibiotics, antituberculosis drugs, antipsychotics, and calcium channel blockers [2]. Despite the fact that amlodipine is generally well tolerated by most people, certain people may experience adverse effects, as is possible with any medicine.

While cutaneous reactions to calcium channel blockers are uncommon, occurring in approximately 8 per million prescriptions, severe reactions like exfoliative dermatitis are even rarer. [3] Specifically, the incidence of exfoliative dermatitis in patients taking anticonvulsants such as phenytoin and carbamazepine is reported to be 3-5% [3-4]. Other drugs associated with exfoliative dermatitis include salazosulfapyridine, azathioprine, and phenobarbital. Tricyclic antidepressants may also induce this condition, similar to phenothiazines [3-4].

Amlodipine is a dihydropyridine analog of nifedipine and has been used worldwide to treat hypertensive patients for over two decades. Amlodipine's long half-life of 30 to 50 hours allows for once-daily dosing, making it a convenient option for managing hypertension and angina [5]. As a calcium antagonist, it lowers blood pressure by inhibiting Ca2+ influx into cells, leading to peripheral arterial vasodilation. The most common side effects are dose-dependent and related to its mechanism of action as a calcium antogonist, such as vasodilation presenting as leg oedema, flushing, telangiectasia or headache. Potential side effects of amlodipine also include skin-related issues, such as rash or dermatitis [5].

## Case presentation

A 71-year-old woman was recently diagnosed with a hypertensive crisis complicated with congestive cardiac failure. During her hospital stay, she was treated with intravenous antihypertensive and diuretic. She was then and stabilized with oral amlodipine, spironolactone, aspirin, atorvastatin, and frusemide and was discharged well. However, one week later, she developed a gradual onset of generalized, diffused, pruritic, erythematous, and scaly skin lesions that initially appeared on both limbs and later spread to the trunk. The was no history of atopy and drug allergies. On examination, she appeared well and was afebrile, with normal vital signs and no signs of angioedema. Examination of her limbs and trunk showed diffuse, dry, scaly skin with generalised erythema. Other systemic examinations were unremarkable. She visited many clinicians for her skin lesions post discharge, and was treated as an eczema flare, yet the lesions were getting worse. She was subsequently referred to the dermatology department and was diagnosed with skin eruption secondary to amlodipine. As a result, amlodipine was abruptly discontinued, and Bisoprolol was initiated. At her follow-up visit to the dermatology clinic one month later, her skin condition had gradually improved.

## Discussion

Generalized Exfoliative Dermatitis (GED) is a rare dermatosis characterized by the development of erythema, scaling, and shedding of the skin. This rare condition may occur in a variety of underlying diseases and can be associated with life-threatening events. The clinical presentation of GED is variable, fluctuates throughout the disease, and progresses insidiously [6].

The progression of disease can be described in the following phases:

1. Chronic phase: Mild scaling of the scalp, anogenital region, inner thigh, axillary region, retroauricular area, and other skin folds.
2. Pruritic phase: Itching and scratching involving the upper and lower extremities, back, neck, and malar area.
3. Exfoliative dermatitis: Sharply marginated, elevated, well-defined erythematous plaques on the trunk and extremities that may fissure, bleed, and drain serous fluid.
4. Resolution phase: Improvement and resolution of lesions after weeks to months of treatment [7].

Drug-induced GED is characterized by keratinocyte apoptosis and loss of epidermal integrity. The underlying mechanisms include drug-specific immune activation, which may trigger a cascade of inflammatory events, keratinocyte apoptosis, dysregulation of pro-inflammatory cytokines and chemokines, and disturbed interaction between keratinocytes and infiltrating cells [6,7]. Calcium channel blockers may induce keratinocyte apoptosis by increasing intracellular calcium levels and activating calcineurin and glycogen synthase kinase 3, which lead to the activation of apoptosis-related factors that destabilize mitochondrial membranes, including altered expression of Bcl-2 family proteins and release of cytochrome C [6,7].

Amlodipine is a calcium channel blocker commonly used in treating hypertension, which can result in skin adverse effects. Calcium is crucial for various cellular functions, including the proliferation and differentiation of keratinocytes, transmission of nerve impulses, release of neurotransmitters and hormones, and contraction of smooth and cardiac muscles [8]. It also plays a role in the synthesis of nitric oxide, the secretion of catecholamines, and the release of hormones like insulin. Calcium is essential in maintaining skin barrier function, as calcium levels increase in the skin after birth. In the cornified envelope, free calcium interacts with transglutaminase and involucrin, cross-linking structural proteins. The permeability barrier of normal skin helps maintain hydration, while impairment leads to skin diseases like ichthyosis [8,9]. Oral amlodipine, which acts on L-type voltage-gated calcium channels, significantly inhibits calcium influx in keratinocytes, inducing apoptotic changes. Amlodipine exposure also attenuates epidermal calcium levels and prevents tight junction formation. This inhibitory effect on calcium influx and epidermal calcium levels by oral amlodipine is expected to lead to an impairment of the skin permeability barrier, resulting in transepidermal water loss and the initiation of secondary changes in keratinocytes [2,3,9].

Amlodipine-induced generalized exfoliative dermatitis can lead to severe morbidity and even mortality if not recognized and managed appropriately. At the first step, amlodipine and other possibly offending drugs must be discontinued immediately. Amlodipine-induced generalized exfoliative dermatitis is unlikely to improve until the use of amlodipine is terminated, and alternative treatments are used for hypertension.

Once discontinuation of amlodipine is done, pharmacological agents should be used to manage generalized exfoliative dermatitis. Antihistamines, such as systemic diphenhydramine are the first-line agents to alleviate pruritus. Patients may also find comfort with topical antiseptics and topical steroids. High-potency topical corticosteroids can be effective, with moderate potency steroid creams as symptoms improve. As the skin symptoms improve, lower-potency topical corticosteroids may be substituted. Additionally, are recommended for all patients experiencing dermatitis, crusting, pruritus, or peeling. Emollients, also known as moisturizers, help

restore the skin barrier function by providing hydration and preventing the loss of transepidermal water [9,11]. This is particularly important in exfoliative dermatitis, where the skin barrier is severely compromised. Emollients should be applied once to several times a day to all affected areas. Ointment-based moisturizers can be used as adjunctive therapy [11].

In some cases, dermatologists may evaluate patients for systemic management of generalized exfoliative dermatitis if indicated. Patients may be given systemic steroids as an alternative to immunosuppressive therapies. However, the appropriate use of systemic steroids in generalized exfoliative dermatitis is not clearly defined, and reverse treatment may cause rebound flare-ups of dermatitis.

Systemic therapy is indicated when symptoms are severe and extensive, involving over 30–90% of the skin surface, particularly if accompanied by systemic symptoms such as fever, chills, malaise, or weight loss. It is also necessary in cases associated with underlying conditions, such as psoriasis or cutaneous T-cell lymphoma, where specific systemic treatments or chemotherapy may be required for malignancy-associated erythroderma. Additionally, systemic therapy is crucial in patients at risk of severe complications like dehydration, electrolyte imbalance, secondary infections, or sepsis, stemming from skin barrier disruption, and requires urgent intervention to stabilize the patient and prevent further deterioration.

In severe cases of exfoliative dermatitis, where topical treatments fail to provide desired effects after two weeks, systemic treatments, such as methotrexate, acitretin, cyclosporine, and newer biologic agents could be considered. Methotrexate is the preferred first-line treatment due to its favourable long-term benefit/safety profile and potential for rapid disease control. In patients with poor liver function or hepatic cytotoxicity, acitretin serves as a good alternative in the management of exfoliative dermatitis. In cases resistant to the above systemic treatments, cyclosporine could be considered a successful treatment in some severe cases. However, caution should be exercised due to its potential side effects and monitoring of renal function [4,9,11].

A follow-up plan should be made for patients diagnosed with generalized exfoliative dermatitis. All patients should be educated to seek immediate medical attention for febrile illness, signs of systemic infection, and new-onset, sudden, and severe skin peeling or erythema. Additionally, patients should be advised to avoid taking amlodipine indefinitely, even years after discontinuation.

## Conclusion

It is important to recognize that some patients may develop cutaneous adverse reactions, including severe reactions, from CCBs. Amlodipine, which is commonly used to treat hypertensive patients should be considered a potential culprit for exfoliative dermatitis. Risk factors for amlodipine-induced GED such as gender, underlying medical conditions, and concurrent medications remain undetermined [5,8]. However, dermatological complaints were previously documented in patients concomitantly taking amlodipine and statins [12]. Besides these cases, amlodipine has been noted as a probable cross-reactive contact dermatitis agent. Prompt recognition and discontinuation of the offending drug is crucial in managing drug-induced exfoliative dermatitis. However, diagnosis can be challenging, as it may mimic other dermatological conditions and requires a high index of suspicion, especially when multiple medications are involved. Further research and analysis of demographic variables are needed to better understand the risk factors for amlodipine-induced GED.

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**Conflict of interest**
There is nothing to declare.

**Patients' consent for the use of images and content for publication**
The patient gave verbal permission for the images and case to be used for publication.

**Authors' contribution**
MCM, SCA and SA contributed to the case write up, and literature search. NAA drafted the manuscript. All authors participated in review, editing, and approving on the final version of the manuscript.

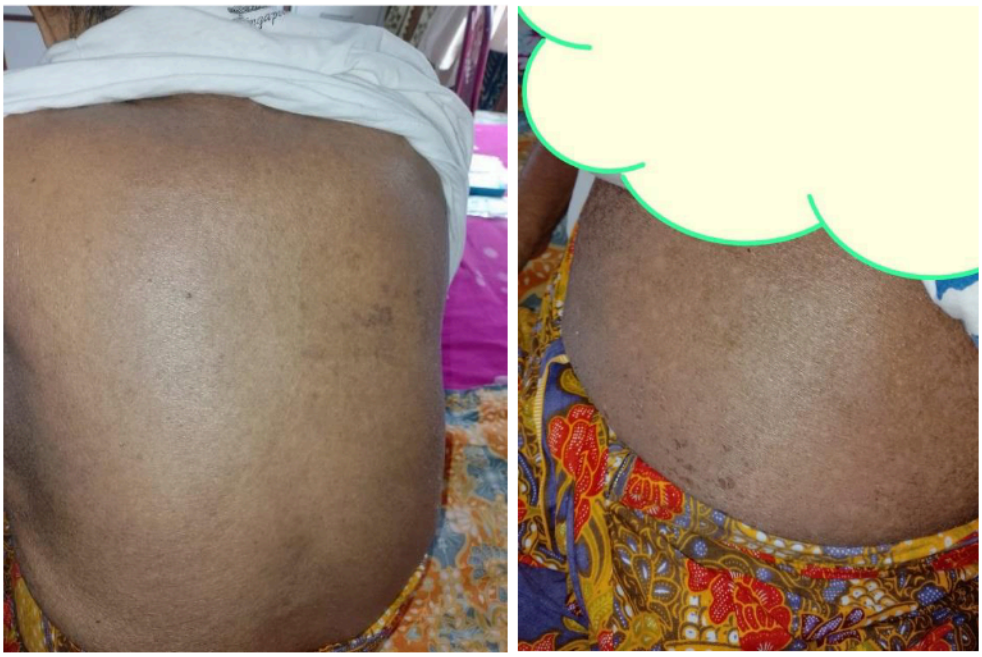

Figure 1. The image shows skin in the area of trunk appears significantly discolored, with darkened patches with texture of the skin is rough and uneven, with prominent scaling and dryness

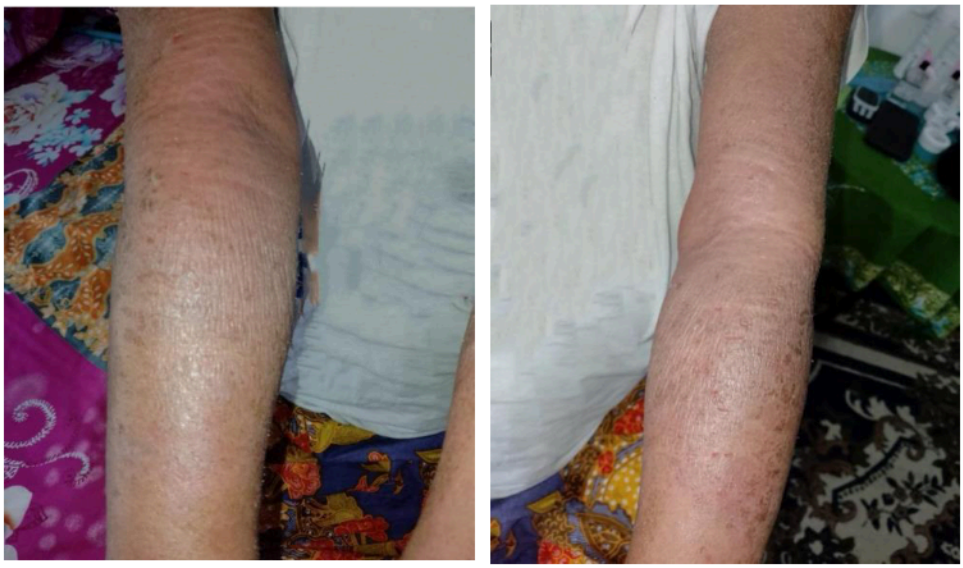

Figure 2. The image shows bilateral hands is dry, with noticeable scaling and a rough texture. There is significant darkening of the skin, indicating hyperpigmentation in the areas affected by the dermatitis.

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