Uncommon Adverse Drug Reaction to a Commonly Used Antihypertensive

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Sir,

Amlodipine, a dihydropyridine calcium channel blocker (CCB) is a widely used antihypertensive drug. Both allergic and nonallergic adverse drug reactions (ADRs) have been reported with amlodipine.[1,2] Serious ADRs such as Stevens–Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN) have been reported rarely in literature.[3] To the best of our knowledge, amlodipine induced generalized bullous fixed drug eruption (GBFDE) is not yet reported in literature.

A 56-year-old male presented to us with multiple fluid-filled lesions all over the body without any oral lesion for past 2 days. He gave a history of dark-colored lesions beneath the blisters forthe last 15–20 days. He was diagnosed as a case of primary hypertension 2 months ago and was started on tablet amlodipine at a dose of 10mg once daily. The patient took amlodipine tablets on and off in the last 2 months. The first episode of fluid-filled lesions occurred after 1 day of ingestion of the drug, following which he had similar 4–5 episodes, which resolved with dark-colored flat lesions over a period of 1 ½ months. He was not on any other concomitant medication.

On cutaneous examination, there were multiple discrete to confluent well-defined erythematous to dusky macules with superimposed bullae present over the face, trunk, upper limbs, and lower limbs [Figure 1a-d]. Multiple well-defined, hyperpigmented macules and patches were present over the periorbital region, bilateral palms, and trunk [Figure 2a-c]. Multiple superficial and few crusted erosions were present over both lips. There was no intraoral and other mucosal involvement. When tangential pressure was applied to theinvolved erythematous areas with the thumb, the shearing force dislodged the upper layers of epidermis from the lower epidermis resulting in the formation of blisters (PseudoNikolsky's sign was positive). General and systemic examination was normal except for high blood pressure. Hematological investigations were normal except for raised creatinine (4.1mg/dl) and urea (88mg/dl) levels. Abdominal sonography revealed grade 2 renal parenchymal disease with calcified granuloma. Other investigations like echocardiography and fundoscopy were normal. Histopathological examination from bullous lesion over the left leg revealed basal cell vacuolation, blister formation with occasional necrotic keratinocytes in epidermis, and pigment incontinence in the dermis, suggestive of bullous FDE [Figure 3a and b]. Based on history, clinical examination, and histopathological findings, a final diagnosis of amlodipine-induced GBFDE was reached. This ADR was reported to the Pharmacovigilance Programme of India (PvPI) (Report no. 2019-53775). Based on the World Health Organization-Uppsala Monitoring Center (WHO-UMC) and Naranjo scale, this ADR was considered as a probable ADR. According to the modified Hartwig and Siegel scale, this ADR fell under a moderate (level 4) category. The patient was managed with oral prednisolone in the dose of 0.75 mg/kg/day tapered over 2 weeks. There was a complete resolution of active lesions with hyperpigmentation [Figures 4a-d and 5a-c]. The patient was referred to the medicine department for alternative antihypertensive drugs and counseled to avoid amlodipine.

Antihypertensive (antiHTN) drugs are frequently prescribed for hypertension and other indications such as migraine, hemangioma, etc. The most common antiHTN drugs to cause cutaneous ADRs

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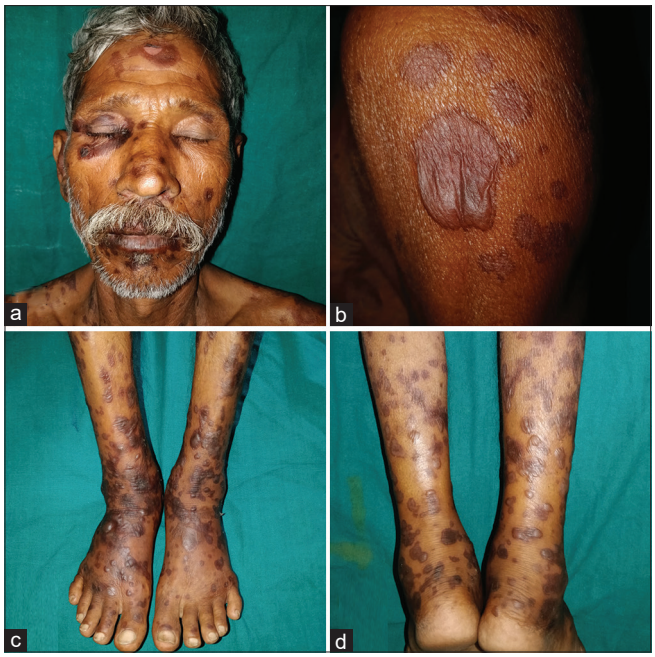

Figure 1: (a-d) Multiple discrete to confluent well defined erythematous to dusky macules and patches with superimposed bullae present over face (a), left arm (b) and lower limbs (c and d)

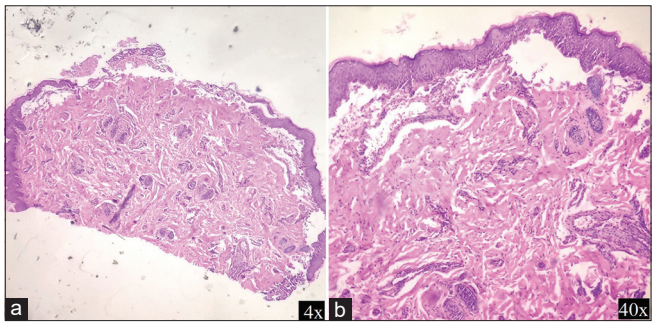

Figure 3: (a and b) Histopathological examination from bullous lesion over left leg revealed, basal cell vacuolation, blister formation with occasional necrotic keratinocytes in the epidermis, and pigment incontinence in the dermis, suggestive of bullous FDE. (H and E, 4×: a and 40×: b)

are angiotensin-converting enzyme inhibitors, CCBs, diuretics, and B blockers.[4] Upadhayai JB *et al*. have reported that among antiHTN drugs, B blockers are more common than CCBs to cause cutaneous ADRs. Urticaria was the most common ADR followed by lichenoid drug eruptions.[5] Danish National Board of Health committee hasreported that 10–60% of reactions caused by antiHTN drugs are dermatological.[6] Both allergic and nonallergic ADRs been reported with the use of CCBs such as flushing (10%), gingival hyperplasia (21%), gynecomastia, facial telangiectasia, photosensitivity, pemphigoid, subacute cutaneous lupus erythematous, erythromelalgia, oral ulcers, granuloma annulare-like reactions, and purpuric exanthema.[1,7]

The more serious cutaneous ADRs associated with the use of CCBs are SJS, TEN,[8] erythema multiforme, and exfoliative dermatitis. A study conducted by Tuchinda

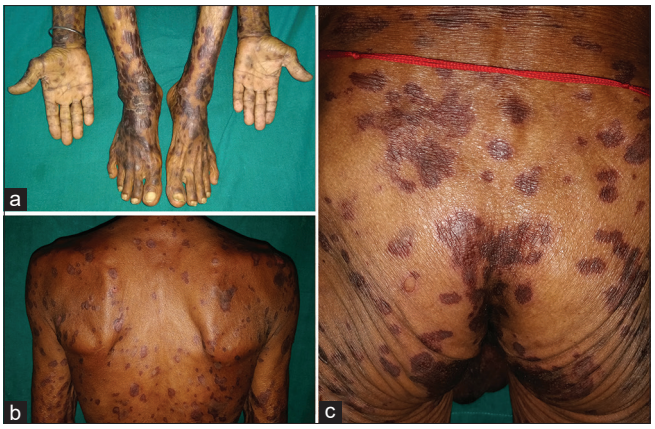

Figure 2: (a-c) Multiple discrete to confluent well defined erythematous to dusky macules and patches over bilateral legs, bilateral palms (a), upper back (b), bilateral buttocks (c)

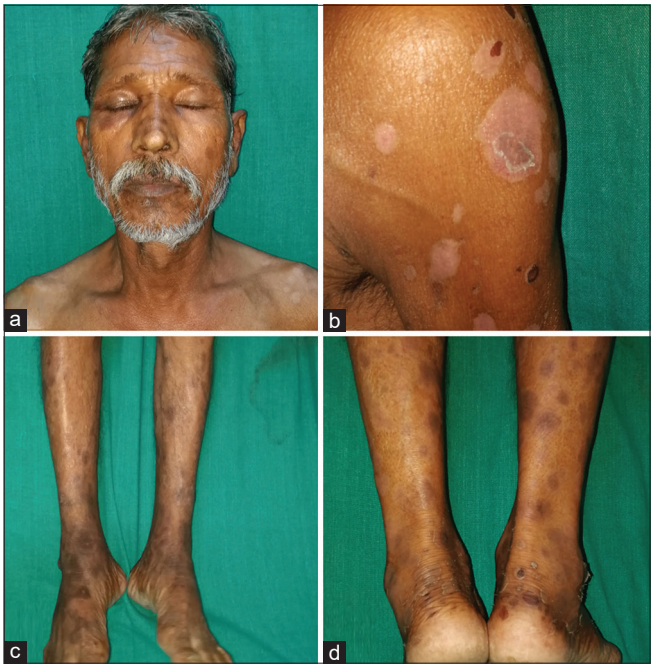

Figure 4: (a-d) Multiple discrete post-inflammatory hyperpigmented macules and patches present over face (a) and left arm (b) and bilateral legs (c and d)

on cutaneous ADRs due to CCB reported that diltiazem was more commonly associated with ADR amongst all CCBs.[3] The maculopapular rash was the most common ADR followed by ankle edema. Amlodipine-induced SJS was reported in 3 (6.2%) patients.

A FDE characteristically occurs at the same site wheneverthedrug is administered. The number of sites affected may increase with each exposure as seen in our patient. Although this ADR is rare, antiHTN like diltiazem and enalapril have been implicated.[9] The commonly affected sites for FDE are the lips, genitals, palms, and soles. After the initial acute phase, residual grayish or slate-colored hyperpigmentation develops. The exact pathogenesis remains obscure but intraepidermal CD8 T

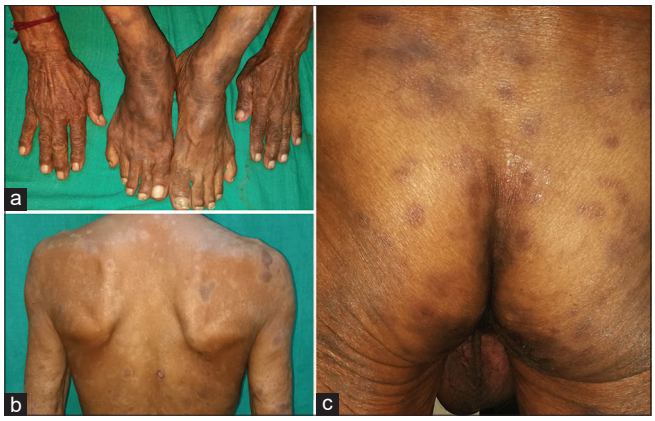

Figure 5: (a-c) Multiple discrete post-inflammatory hyperpigmented macules and patches present over bilateral hands, feet (a), upper back (b), and bilateral buttocks (c)

cells that persist at the previous injury site are implicated in keratinocyte apoptosis.

The closest differential diagnosis for our case was TEN. The differentiating features from TEN include prior history of similar episodes, relatively uninvolvedmucosal surfaces, presence of large blisters with normal intervening skin, and the absence of a purpuric target lesion. Oral stimulation test is the gold standard test for diagnosing FDE. Skin patch test, drug lymphocyte stimulation test, intradermal test, and skin prick test may be useful for the diagnosis. The treatment for GBFDE includes discontinuation of the responsible drug, systemic steroids, cyclosporine, a topical steroid, and wound dressing for the eroded lesions. There are very few case reports of severe cutaneous ADR secondary to amlodipine. This case is reported to create awareness among physicians regarding the development of this severe cutaneous ADR secondary to the commonly used antihypertensive drug, amlodipine.

Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent forms. In the form, the patient(s) has/have given his/her/their consent for his/her/their images and other clinical information to be reported in the journal. The patients understand that their names and initials will not be published and due efforts will be made to conceal their identity, but anonymity cannot be guaranteed.

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Conflicts of interest

There are no conflicts of interest.

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