Symmetrical Drug-Related Intertriginous and Flexural Exanthema Probably Caused by Acyclovir

Dear Editor,

Symmetrical drug-related intertriginous and flexural exanthema (SDRIFE) is a benign, self-limiting type IV drug hypersensitivity reaction characteristically affecting gluteal and intertriginous areas without systemic involvement.[1] The majority of SDRIFE cases are caused by β-lactam antibiotics, followed by chemotherapeutic agents.[2,3]

We describe an uncommon case of SDRIFE, where acyclovir was the probable cause.[4]

A 36-year-old man with chronic myeloid leukemia on Imatinib 300 mg daily for 3 months developed painful oral erosions of 5 days duration and was treated as herpetic gingivostomatitis with oral acyclovir for 5 days. On the second day of acyclovir, he developed itchy lesions over his flexures, which progressed. There was no history of other topical or systemic drug use. He consulted our department on the sixth day of rash after completing the acyclovir course. Physical examination showed sharply demarcated, symmetrical, erythematous, and hyperpigmented papules and plaques with scaling and maceration over flexures of the groin, axilla, cubital fossa, and palmar creases, with a few surrounding lesions [Figures 1 and 2]. Systemic symptoms were not present. Gram staining and potassium hydroxide (KOH) examination ruled out pyodermas and fungal infections. Normal blood counts, liver and renal function tests, chest radiography, and abdominal ultrasound ruled out systemic involvement. Skin biopsy from the axillary lesion showed erosion, crusting, and hyperkeratosis of epidermis with dense, diffuse, and perivascular dermal infiltrate predominantly composed of lymphocytes and eosinophils [Figure 3]. Thus, clinical, laboratory, and histopathological examinations ruled out other differentials, like acute generalized exanthematous pustulosis (AGEP), neutrophilic eccrine hidradenitis (NEH), and eccrine squamous syringometaplasia (ESS), confirming SDRIFE.

Imatinib was stopped and lesions resolved after 10 days with topical corticosteroids. The World Health Organisation-Uppsala Monitoring Centre (WHO-UMC) scale and Naranjo's algorithm (score 7) indicated the likelihood of acyclovir being the cause as "probable." Imatinib was restarted 1 week after resolution of the rash, but there was no recurrence.

Patch testing with 20% acyclovir in petrolatum done on the patient's back (nonlesional area) 1 month later was negative. The patient refused oral provocation testing.

Drug-related eruptions involving the buttocks and flexural folds after systemic drug exposure were initially termed

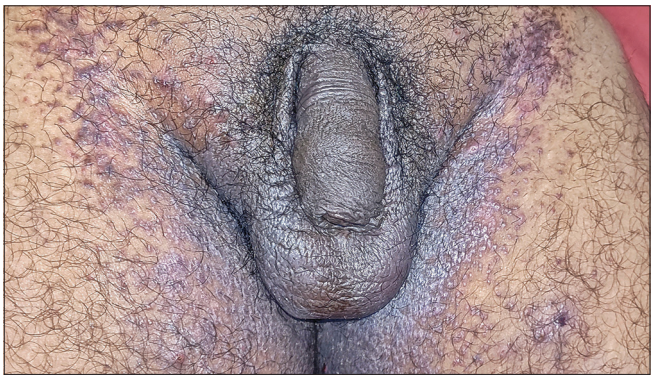

Figure 1: Symmetric, erythematous, and hyperpigmented confluent papules and plaques with scaling and maceration over inguinal folds and medial thighs

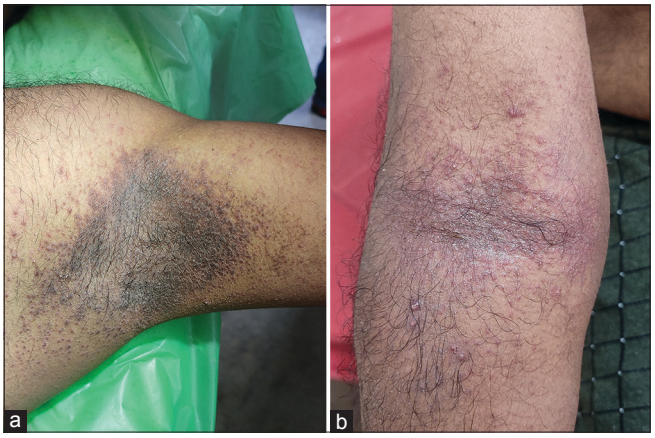

Figure 2: (a) Confluent macerated erythematous and hyperpigmented papules and plaques over left axilla (b) Multiple confluent erythematous papules with scaling over right cubital fossa

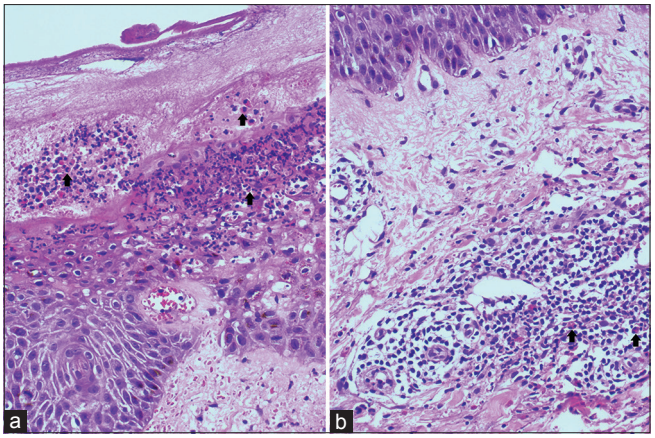

Figure 3: (a) Hyperkeratosis, crusting, upper dermal edema, dilated capillaries, and eosinophilic infiltrate (black arrows) (H and E, ×100) (b) Irregular epidermal hyperplasia with middermis showing scattered and perivascular infiltrate of lymphocytes and eosinophils (black arrows) (H and E, ×100)

drug-related baboon syndrome[5] and those not requiring prior sensitization were later renamed SDRIFE.[1]

The diagnostic criteria for SDRIFE include[1]: 1) exposure to a systemically administered drug (excluding contact allergens), 2) sharply demarcated erythema involving the gluteal, perianal, inguinal, or perigenital areas, 3) involvement of at least one other intertriginous area, 4) symmetry, and 5) absence of systemic symptoms and signs. All these features were present in this patient.

The flexural predilection in SDRIFE may be due to recall phenomenon from previous mechanical stimulation or intertrigo, or preferential sweat gland excretion of certain drugs.[3]

SDRIFE has a short latency of 2–5 days due to drug directly binding to T-cell receptors.[2,3]

Acyclovir and its prodrug valacyclovir, are commonly used antiviral drugs against human herpes viruses. This patient had received acyclovir for 2 days before developing the rash, which is typical of SDRIFE. Imatinib was not considered as a cause since the latent period between imatinib intake and onset of symptoms was longer than usually seen in SDRIFE, lesions resolved after discontinuing acyclovir, and there was no recurrence after restarting imatinib.

The histopathology of SDRIFE includes superficial perivascular lymphocytic infiltrate and dermal eosinophils, as seen in this patient.[2,3] SDRIFE is diagnosed clinically and a biopsy helps exclude other intertriginous eruptions.[2,3]

Other drug rashes with intertriginous involvement include AGEP, NEH and ESS. Compared to AGEP, SDRIFE has fewer lesions, flexural localization, and lacks systemic features.[1,5] NEH and ESS are chemotherapy-related reactions affecting eccrine sweat glands. The presence of typical histopathological features like epidermal dysmaturation and eccrine squamous syringometaplasia, as well as the absence of striking symmetry, distinguishes these conditions from SDRIFE.[2,5] Apart from gram stain and KOH examination, SDRIFE can be distinguished clinically from tinea cruris by the advancing scaly borders; from candidiasis by peripheral satellite pustules and from streptococcal intertrigo by bright red eroded plaques with oozing.[5] Nail changes in inverse psoriasis; yellowish greasy scaling involving nonflexural sites in seborrheic dermatitis; flaccid blisters or erosions in Hailey–Hailey disease; vegetating plaques in pemphigus vegetans and their specific histopathological findings differentiate those conditions from SDRIFE.[1,3,5]

Intradermal skin tests, patch tests, and lymphocyte transformation tests are inconsistent and appear to be drug-specific, limiting their diagnostic utility, as seen in the previous case of SDRIFE with valacyclovir.[3,4] The mainstay of management is symptomatic treatment, drug withdrawal, and future drug avoidance.[3]

Despite numerous reports of other drug eruptions caused by systemic acyclovir and/or valacyclovir, SDRIFE with acyclovir is uncommon.[4]

This case highlights the importance of being aware that even commonly prescribed drugs like acyclovir can cause SDRIFE.

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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