

CONTACT POINT

Paracetamol-induced symmetrical drug-related intertriginous and flexural exanthema (SDRIFE) in a psoriasis patient receiving apremilast therapy

Matteo Megna¹  | Eleonora Cinelli¹ | Maddalena Napolitano²  |
Gabriella Fabbrocini¹ | Cataldo Patruno³ 

¹Department of Dermatology, University of Naples Federico II, Napoli, Italy

²Department of Medicine and Health Sciences Vincenzo Tiberio, University of Molise, Campobasso, Italy

³Department of Health Sciences, University Magna Graecia, Catanzaro, Italy

Correspondence

Dr Matteo Megna, Department of Dermatology – University of Naples Federico II, Via Pansini, 5 80131 Napoli, Italy.

Email: mat24@libero.it

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Symmetrical drug-related intertriginous and flexural exanthema (SDRIFE) is a cutaneous adverse reaction symmetrically involving the gluteal and intertriginous areas.¹ Many different drugs have been implicated as causing SDRIFE,^{1–3} most commonly antibiotics. Nonsteroidal anti-inflammatory drugs (NSAIDs) are also a common elicitor,^{4,5} whereas only one case of paracetamol-induced SDRIFE has previously been reported.⁶ Moreover, to date, no case of SDRIFE in patients taking apremilast, a small molecule that inhibits phosphodiesterase 4 (PDE4) and is approved for treatment of psoriasis and psoriatic arthritis,⁷ has been described.

CASE REPORT

A 62-year-old woman was referred to our outpatient clinic for erythematous patches symmetrically located at axillary areas, inguinal folds, sub-mammary areas, and nape. She had been taking apremilast 30 mg twice daily for 6 months to treat longstanding plaque psoriasis, achieving adequate disease control. Her medical history was positive for chronic hepatitis C infection (genotype 1B) treated with sofosbuvir + daclatasvir for 12 weeks, achieving a complete and persistent hepatitis C virus eradication. At the time of referral to our clinic, the patient was not taking any medications except apremilast.

Examination revealed sharply demarcated erythematous patches of irregular oval shape, ranging from 8 to 17 cm, symmetrically located at the posterior face of the neck, the axillae, inguinal folds, and sub-mammary areas (Figure 1). Intense itching and burning were reported. The patient reported onset 1 day after intake of

paracetamol 1000 mg for a headache. Previously she had tolerated the same drug well. Routine blood tests were within normal ranges. Histological examination of a lesional punch biopsy showed superficial perivascular infiltrate, extravasated erythrocytes, neutrophils, and eosinophils with mild dermal oedema and slight spongiosis. Basing on these findings, SDRIFE was diagnosed. Apremilast treatment was not discontinued due to the lack of chronological correlation. Topical treatment with zinc oxide led to the complete resolution of the skin lesions in only 10 days (Figure S1.). The patient is still receiving apremilast treatment; at 10 months follow-up, no new skin lesions have developed.

DISCUSSION

Baboon syndrome was first described in 1984 by Andersen et al as a specific skin eruption (erythema of buttocks and upper inner thighs) that resembled the red gluteal area of baboons and occurred after systemic exposure to contact allergens.⁸ This reaction was originally noted in three patients previously sensitized by topical contact upon subsequent systemic exposure to the same substance (mercury, nickel, and ampicillin, respectively).⁸ Baboon syndrome was therefore considered a systemic allergic dermatitis. In 2004 Häusermann et al reviewed all 42 of the published drug-related cases of Baboon syndrome elicited by systemic administration of either oral or intravenous drugs, mainly without prior sensitization.¹ Given the distinctive clinical features of these drug-related eruptions, the authors coined the term SDRIFE to specifically refer to this condition, which encompasses the



FIGURE 1 Sharply demarcated erythematous patches symmetrically located at the posterior face of the neck, axillae, inguinal folds, and submammary areas

concept of drug-related Baboon syndrome.¹ SDRIFE is considered a rare, benign, and often underdiagnosed drug eruption that usually appears between a few hours and a few days after drug assumption.¹ Many different drugs can induce this particular adverse reaction, including antibiotics (eg, amoxicillin, ampicillin, amoxicillin/clavulanic acid, ceftriaxone, etc), antiviral agents (valacyclovir), nonsteroidal (NSAIDs) and steroidal anti-inflammatory drugs, and other pharmacological classes (eg, heparin, hydroxyurea, allopurinol, mitomycin C, etc).^{2,6} The most common culprits are antibiotics, particularly beta-lactams,² or analgesics, especially NSAIDs including COX-1 and/or COX-2 inhibitors (celecoxib, etoricoxib, mefenamic acid, and naproxen).^{2,4,5} Conversely, only one case of paracetamol-induced SDRIFE has been described so far in the literature; it occurred in a 33-year-old woman and completely resolved after 10 days of systemic corticosteroids.⁶ In our patient, SDRIFE completely resolved after a 10-day-course of topical zinc oxide.

Even if our patient was receiving apremilast treatment when she took paracetamol, she had been taking apremilast for 6 months at the time of SDRIFE onset. Moreover, no case of SDRIFE while receiving PDE4 inhibitor therapy has been reported in the literature.

Conversely, the latency between paracetamol intake and onset of SDRIFE in our patient (1 day) is typical for this disease.¹ Hence, we excluded apremilast as the responsible agent, and the treatment was thus continued. However, we are unsure if any kind of relationship between apremilast, paracetamol intake, and SDRIFE exists, that is, whether apremilast could have facilitated the patient's reaction to paracetamol.

The pathogenesis of SDRIFE still needs to be fully elucidated, notwithstanding different hypothetical mechanisms. For instance, type IV or T-cell mediated delayed hypersensitivity, with features of both type IVa (Th1 and macrophages) and type IVc (CD8+ T cells), has been hypothesized.⁹⁻¹² However, not all the reported cases can be explained, as the reaction can also develop 1 hour after drug administration, and not all patients had been previously sensitized.² Therefore, other authors have suggested recall phenomena: some cases could be a "recall" of a previous cutaneous injury (eg, severe diaper rash in infancy, contact dermatitis caused by any allergen or irritant, or other forms of typical intertrigo) with different or identical related agents.^{13,14} Moreover, a recent theory suggested the p-i concept (pharmacological interaction with immunoreceptors) as a possible

mechanism.¹⁵ This phenomenon would imply a direct binding of drugs to a suitable T-cell receptor (TCR) without the need for major histocompatibility complex presentation and without preceding metabolism.¹⁵ In our case, the patient reported that she had previously used paracetamol several times without any problems; neither did she report any adverse events linked to apremilast use. Therefore, a hypothetical interaction between these two drugs cannot definitively be excluded. According to the above-cited hypothesis, a p-i interaction between paracetamol and a TCR which apremilast treatment could have favoured by modulation of immunity and T cells can not be excluded. Indeed, PDE4 inhibitors have major effects on T cells, reducing the production of Th1, Th2, and Th17 cytokines.⁷ These anti-inflammatory effects may have enhanced other T-cellular pathways, leading to a fitting TCR–paracetamol binding (the p-i concept), possibly influencing patient susceptibility to paracetamol.

In conclusion, we report a case of SDRIFE caused by paracetamol in a patient receiving apremilast therapy. Future studies should investigate possible interactions between different drugs (eg, apremilast and paracetamol) and TCRs.

CONFLICTS OF INTEREST

None to declare.

ORCID

Matteo Megna  <https://orcid.org/0000-0003-1803-2046>

Maddalena Napolitano  <https://orcid.org/0000-0003-3309-8190>

Cataldo Patruno  <https://orcid.org/0000-0001-8661-2822>

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SUPPORTING INFORMATION

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