SHORT COMMUNICATION

Persistent Symmetrical Drug-related Intertriginous and Flexural Exanthema (SDRIFE) Caused by Metoprolol: Resolution via Beta-blocker Switch

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Symmetrical drug-related intertriginous and flexural exanthema (SDRIFE), previously known as "baboon syndrome," is a rare and distinctive drug induced reaction characterized by sharply demarcated erythema symmetrically affecting intertriginous and flexural areas (1–4). The most commonly reported triggers include β-lactam antibiotics, macrolides and iodinated radiocontrast agents. Numerous other drugs, including analgesics, antihypertensives, antifungals and proton pump inhibitors, have also been reported for the induction of SDRIFE (5). Pathophysiology is thought to involve a drug-specific delayed-type hypersensitivity reaction (type IV) mediated predominantly by Th1- and possibly Th17-cells, with preferential homing of effector memory T cells to flexural skin (6, 7).

Histopathology of SDRIFE is often nonspecific or shows a combination of different histopathological patterns, most commonly interface, spongiotic and psoriasiform changes (8).

We report a case of initially unrecognized metoprolol induced SDRIFE, characterized by delayed resolution after drug discontinuation and the absence of recurrence following a switch to bisoprolol.

CASE REPORT

A 59-year-old woman presented with progressive erythematous skin lesions over a 7-month period, involving the inguinal region and subsequently spreading symmetrically to flexural areas (axillae, abdominal and gluteal folds). Clinical examination revealed well-demarcated erythematous-to-brownish plaques with scaling and an atrophic appearance in the aforementioned locations (**Fig. 1**). Severe burning and pruritus, significantly impairing daily activities were reported. Previous treatments, including topical and systemic antifungals, antibiotics and corticosteroids, failed to provide significant improvement; oral prednisolone induced only transient remission, with recurrence upon dose tapering. Initial histopathological examination demonstrated a superficial perivascular lymphocytic infiltrate. Repeated biopsies obtained from different sites (total n=4) revealed serocrustous intracorneal inclusions, parakeratosis, acanthosis, spongiosis and a lymphohistiocytic infiltrate with focal leukocyte accumulation in the upper dermis (Fig. 1d). These findings were consistent with subacute dermatitis and helped exclude differential diagnoses such as psoriasis inversa, candidal intertrigo, Hailey–Hailey disease and cutaneous T-cell lymphoma. The patient denied the use of new topical products, deodorants, hair removal agents, detergents or recently purchased clothing. Shortly after symptom onset, she discontinued a recently prescribed antidepressant (agomelatine), although this resulted in no clinical improvement. No other new medications were initially reported. Her medical history was notable for hypertension, hyperlipidemia and vitamin D deficiency. Regular medications included metoprolol, lercanidipine, candesartan, atorvastatin and vitamin D supplementation.

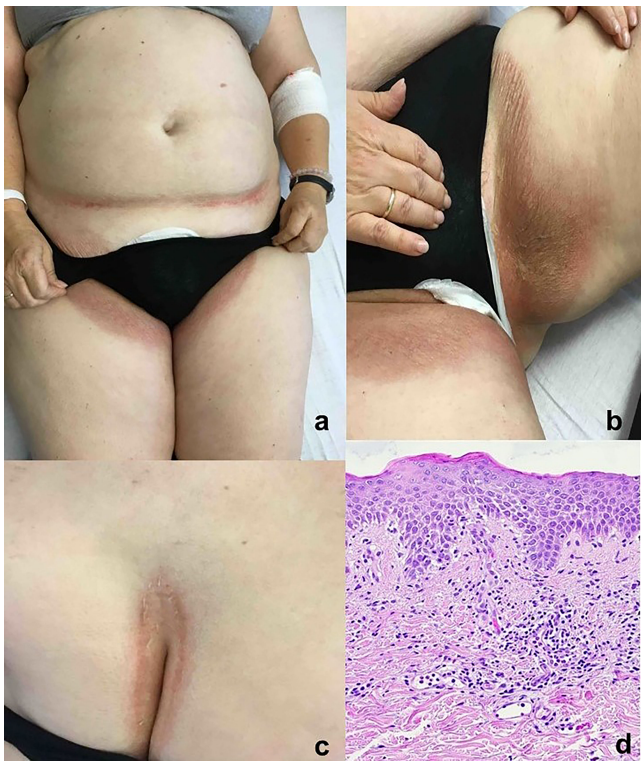

Fig. 1. Cutaneous and histological findings at initial presentation. Well-demarcated erythematous-to-brownish scaly plaques with an atrophic appearance involving the (A) lower abdominal fold, (B) groin, (C) gluteal fold. (D) Hematoxylin and eosin (H&E) staining demonstrating nonspecific parakeratosis, acanthosis, spongiosis, dermal lymphocytic infiltrates and neutrophilic granulocytes within the blood vessels of the upper dermis (original magnification, ×200).

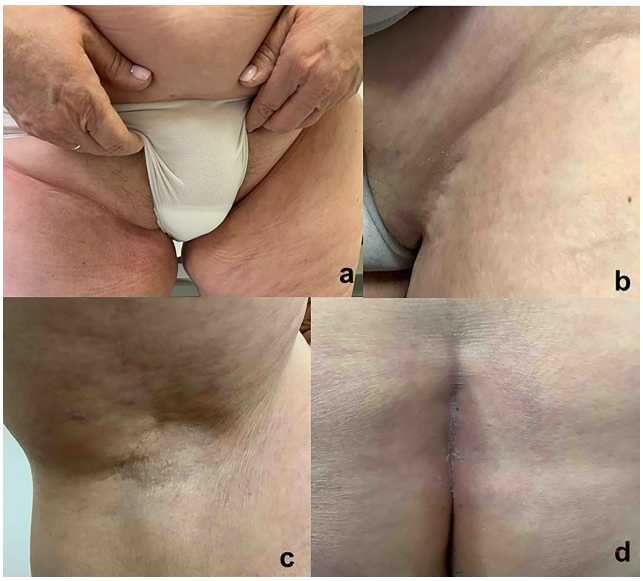

Fig. 2. Cutaneous findings 8 weeks after metoprolol discontinuation and 2 weeks after bisoprolol initiation. Complete remission of cutaneous findings in the (A) groin area, (B) left groin, (C) right axilla and (D) gluteal fold.

Given the symmetrical intertriginous distribution, chronic course and steroid-responsive yet recurrent nature of the lesions, SDRIFE was suspected despite nonspecific eczematous histological findings. A detailed review of the medication history subsequently revealed that metoprolol had been initiated less than 2 weeks prior to lesion onset.

Metoprolol was discontinued upon clinical suspicion. Complete resolution of the lesions, including remission of erythema, scaling and subjective symptoms, was observed only after 5–6 weeks of follow-up. Due to a post-cessation increase in blood pressure, therapy was subsequently switched to bisoprolol. Two weeks after the switch, no recurrence of SDRIFE was observed (**Fig. 2**), and at the 6-month follow-up, the patient remained symptom-free (**Fig. 3**).

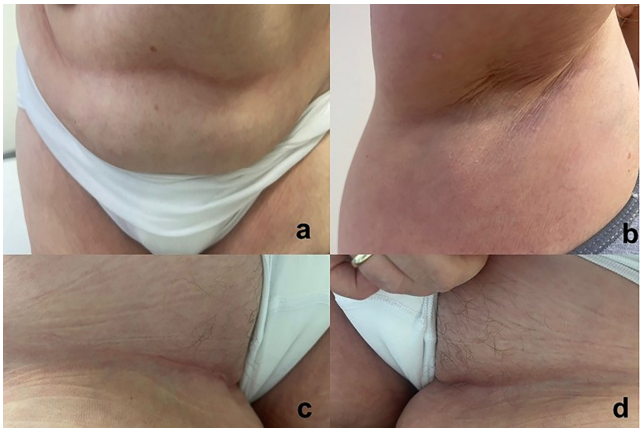

Fig. 3. Cutaneous findings 6 months after metoprolol discontinuation and 4,5 months after bisoprolol initiation. Complete remission of cutaneous findings without signs of relapse (A) groin area, (B) right axilla, (C) right groin and (D) left groin.

DISCUSSION

This report highlights several clinically relevant aspects of SDRIFE. The diagnosis was based on established criteria, including symmetrical, sharply demarcated erythema of the gluteal/perianal region and/or V-shaped erythema of the inguinal/perigenital area, involvement of at least one additional intertriginous or flexural site, absence of systemic symptoms and exposure to a systemically administered drug (first or repeated dose), while excluding contact allergens and alternative diagnoses (2). Notably, the morphology of skin lesions in SDRIFE can vary considerably. For example, a pustulobullous variant has previously been reported in a patient from Sri Lanka following cefuroxime exposure (9).

Moreover, histopathological findings in SDRIFE are often nonspecific and may resemble those of other drug-induced exanthems, typically showing superficial lymphocytic infiltrates, spongiosis and parakeratosis. In a clinicopathological analysis of 19 cases, Schuler et al. identified antibiotics as the most frequent triggers of SDRIFE and expanded the spectrum of reported causative agents. Histologically the eruption most commonly demonstrated a superficial perivascular lymphocytic infiltrate accompanied by dermal eosinophils and spongiosis. Less frequent findings including basal vacuolization, apoptotic keratinocytes, interstitial histiocytes and rare atypical features such as flame figures, further illustrate the broad histopathological spectrum and emphasize the importance of clinicopathological correlation (8, 10). In our patient, repeated biopsies revealed findings consistent with subacute dermatitis but were not of diagnostic help. Therefore, histopathology mainly serves to exclude differential diagnoses, such as psoriasis inversa, candidal intertrigo, Hailey–Hailey disease or cutaneous T-cell lymphoma. Careful clinical evaluation and a detailed medication history remain essential for diagnosis.

Importantly, SDRIFE should be considered in the differential diagnosis of any symmetrical intertriginous eruption. Early recognition is essential, as accurate diagnosis and prompt withdrawal of the causative drug are crucial to minimize prolonged impairment of the patient's quality of life (11). Although SDRIFE typically resolves spontaneously within 1–2 weeks after discontinuation of the suspected culprit drug (5), our case demonstrated a more protracted course. The delayed diagnosis was likely related to the patient's initial failure to report the introduction of the culprit medication, compounded by the non-specific histological findings, which did not arouse suspicion of a drug-related eruption. These factors may have contributed to the apparent treatment resistance and delayed remission. Notably, the skin lesions persisted

for 5–6 weeks, and the patient remained symptomatic with no reduction in symptom intensity at her visit 4 weeks after drug withdrawal. This case underscores the importance of considering delayed resolution when assessing drug causality; despite the prolonged clinical course, the close temporal relationship strongly supports metoprolol as the causative agent.

Cardiovascular drugs, including β-blockers, are rarely implicated as triggers of delayed-type cutaneous hypersensitivity reactions (12). Reported manifestations include fixed drug eruptions (FDE), lichenoid drug eruptions (LDE), morbilliform exanthems – including specialized variants like acute generalized exanthematous pustulosis (AGEP) although the available evidence is largely limited to isolated case reports. Metoprolol-induced SDRIFE has been described only once, in a review of 19 novel cases by Schuler et al. (10). However, such cases may be underreported, as SDRIFE is often rapidly recognized as a drug-related adverse reaction because of its characteristic presentation, prompt onset after drug exposure and typically favorable course following drug discontinuation.

Regarding the transition from metoprolol to bisoprolol, although both are selective β-adrenergic antagonists, they differ structurally and pharmacokinetically. Metoprolol is a lipophilic aryloxy-propanolamine derivative with moderate β1-selectivity and is primarily metabolized via CYP2D6, an enzyme with clinically relevant genetic polymorphisms. In contrast, bisoprolol is more hydrophilic, exhibits greater β1-selectivity and undergoes balanced renal and hepatic elimination by CYP3A4 (13, 14). Collectively, structural, functional, physicochemical and metabolic differences may reduce the likelihood of immunological cross-reactivity, particularly with regard to delayed hypersensitivity reactions.

T-cell-mediated cutaneous reactions to β-blockers are exceedingly rare; consequently, potential cross-reactivity between different β-blockers has not been systematically investigated, remains poorly defined and appears to be inconsistent and unpredictable (15). In our patient, no recurrence was observed after initiation of bisoprolol, suggesting that switching to an alternative β-blocker may be feasible. At the 6 month follow-up, the patient remained symptom-free.

In conclusion, SDRIFE should be considered in the differential diagnosis of symmetrical, therapy-resistant intertriginous eruptions. Histopathological findings are often nonspecific and mainly serve to exclude differential diagnoses. This case highlights the importance of a thorough medication history and careful assessment of the temporal relationship between drug exposure and symptom onset, which remain essential for diagnosis. β-blockers, including metoprolol, may trigger SDRIFE, whereas switching to structurally distinct agents such as bisoprolol may be feasible under close monitoring.

The authors have no conflicts of interest to declare.

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