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CLINICAL LETTER

Rare case of itraconazole induced SDRIFE (symmetrical drug-related intertriginous and flexural exanthema)

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Dear Editors,

A 53-year-old male patient had been suffering from perianal dermatitis for 6 months with recent mycotic superinfection (*Candida albicans*), which had been treated with topical antimycotics (nystatin) in combination with zinc ointments as well as topical glucocorticosteroids (Figure 1). As the dermatitis showed no remission, itraconazole 100 mg once daily was added to the therapeutic regimen for 9 days. The patient then started to notice an exacerbation and progressive weeping of the perianal rash as well as new lesions in the inguinal and axillar region.

Upon examination, the patient showed symmetrical bilateral erythemas of the inguinal and axillar regions as well as macerations and erosions, particularly on the buttocks and in the inguinal folds (Figure 1). Mucous membranes were unremarkable. The patient showed normal vital signs and did not show any symptoms of systemic involvement.

Two punch biopsies were taken from axillary and gluteal lesions on the day of hospitalization. The biopsy taken from the axillary region showed hyperkeratosis and acanthopapillomatosis. A marked spongiosis as well as vacuolar interface dermatitis was visible. In addition, individual parakeratotic cones were detectable. The upper corium showed marked edema with increased eosinophilic granulocytes (Figure 2a). Overall, the findings were consistent with a drug reaction. The biopsy taken from the gluteal region showed orthokeratosis, an acanthotic epidermis with spongiosis. Moreover, the upper corium showed increased neutrophilic granulocytes (Figure 2b). The findings were consistent with hematogenous contact dermatitis. Periodic acid-Schiff (PAS) staining was unremarkable. Differential blood count showed only slight leukocytosis and no elevation of eosinophiles.

Upon oral treatment with prednisolone 1 mg/kg/ bodyweight (BW) per day and topical treatment with diflucortolone valerate 0.1%, the patient improved within 2 days. Adjunctive therapy consisted of disinfecting agents (polyhexanide and phenol-methanal uric acid bathing) as well as analgesic treatment with metamizole.

The exanthema had severely abated at day six of treatment. The dose of prednisolone could be tapered quickly, and after 17 days the patient showed complete remission of itraconazole-induced symmetrical drug-related intertriginous and flexural exanthema (SDRIFE).

Symmetrical drug-related intertriginous and flexural exanthema is characterized by the eruption of a benign dermatitis, particularly in the intertriginous, inguinal, and gluteal areas. This particular macular rash is commonly caused by systemic drugs such as antibiotics, for instance amoxicillin and clindamycin, antimycotics, as well as certain cytostatics, urostatics, contrast agents and anticoagulants. The rash develops without any previous sensitization and usually starts within hours up to 2 days after the first drug administration.[1,2] Typical antimycotics reported to cause SDRIFE include terbinafine, nystatin, and fluconazole.[3–5]

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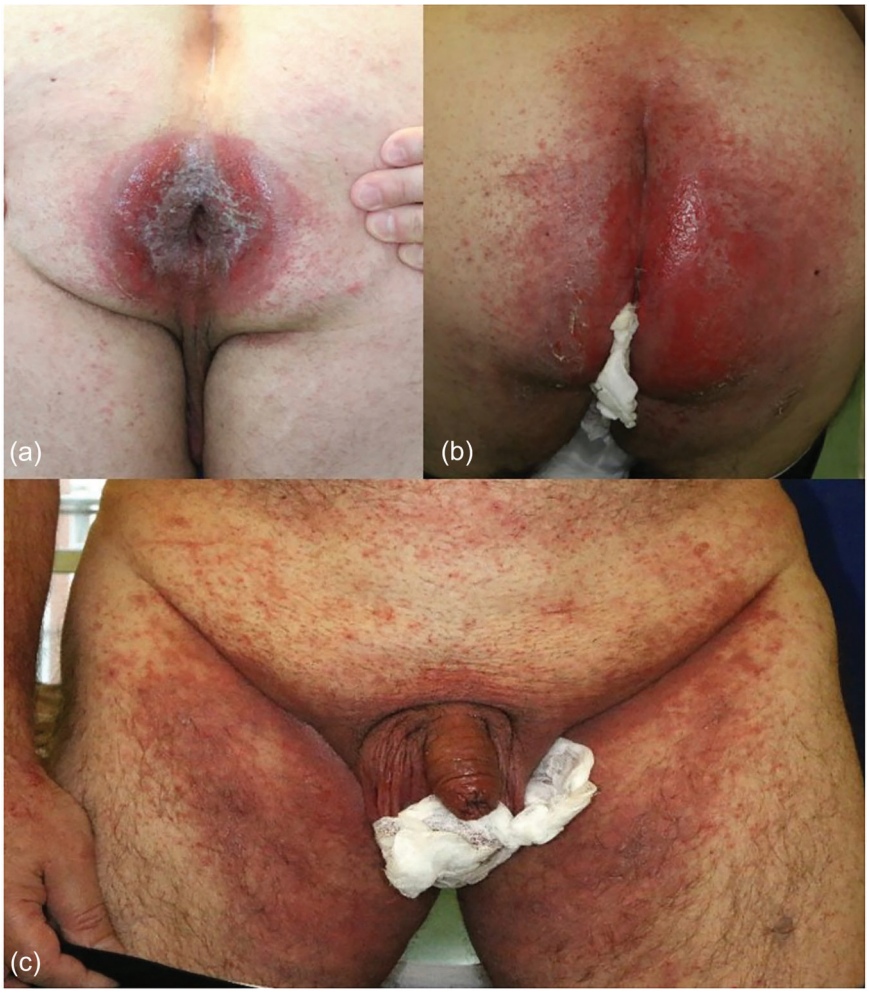

FIGURE 1 Clinical Picture. (a) Perianal dermatitis and candida superinfection. (b) Symmetrical gluteal erythema with erosions. (c) Typical symmetrical erythema of the inguinal region.

Only very few cases in the literature have hitherto suggested that itraconazole may cause SDRIFE.[4,6] In their case series of twelve patients from eastern India, Hassanandani et al. proposed a correlation between itraconazole and SDRIFE due to the prevalent use of the drug in light of rising incidence of dermatophytoses in the region.

Clinically, the symmetrical erythema is often described to be associated with oozing and sometimes with papules causing itch, pain, and discomfort, while bullae are rare. SDRIFE neither affects palmoplantar surfaces nor the face.[7,8] Diagnostic criteria suggested by Häusermann et al. include exposure to a systemic drug, erythema of the gluteal or perianal area, V-shaped erythema of the inguinal area, involvement of at least one other intertriginous body site, symmetry of the affected areas, and absence of systemic toxicity.[5] Even though guidelines for epicutaneous patch tests suggest this diagnostic tool in SDRIFE, the *Oxford Centre for Evidence-Based Medicine* only provides mechanism-based reasoning for this disease, with no systematic reviews or clinical studies proving the benefit of an allergological work-up. Since a prior sensitization is not essential in SDRIFE, we decided not to perform an epicutaneous patch test with our patient who presented characteristic clinical findings.[9] Differential blood count should exclude leukocytosis which can be seen with "acute generalized exanthematous pustulosis" (AGEP) and eosinophilia, present in "drug rash with eosinophilia and systemic symptoms" (DRESS). Histologic features of SDRIFE include superficial perivascular lymphocytic infiltrate, sometimes with neutrophils and lymphocytes, although these findings are not specific.[5] Fever, abrupt onset of non-follicular pustules, and edema of the face and hands suggest systemic involvement and point towards initial stages of "severe cutaneous adverse reactions" (SCAR) such as AGEP or DRESS. Other dermatoses with a predilection for intertriginous areas should be ruled out. While satellite lesions and odor may indicate cutaneous infections or Morbus Hailey Hailey, a history of previously applied topical agents may indicate a contact allergy.[10] Other differential diagnoses of SDRIFE include moisture-associated-skin damage, intertrigo, tinea, psoriasis inversa, eccrine squamous syringometaplasia, neutrophilic eccrine hidradenitis and staphylococcal scalded skin syndrome.[10]

Symmetrical drug-related intertriginous and flexural exanthema was formerly considered as fixed drug eruption. The location-specific rash known as "baboon syndrome" was associated not only with systemic drugs but also with hematogenous contact eczema. This association

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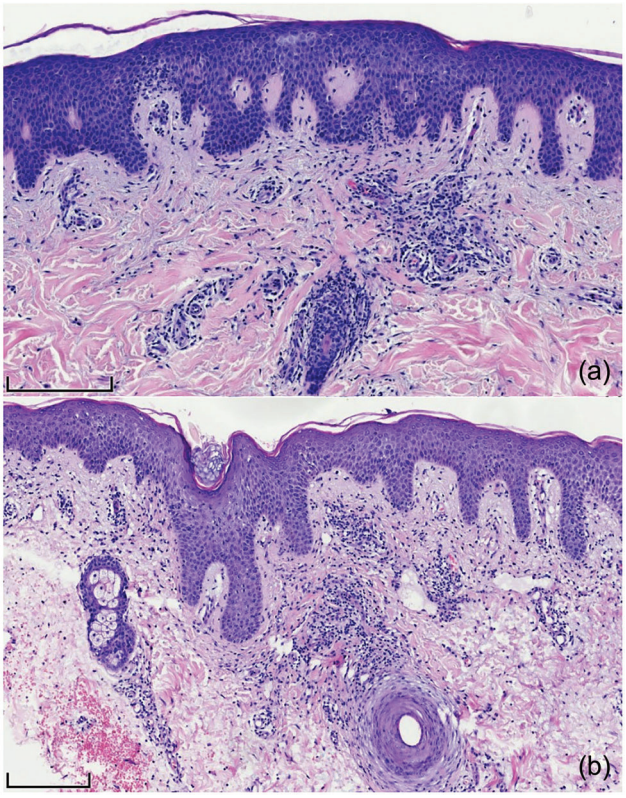

FIGURE 2 Histology. (a) Axillary Biopsy showing hyperkeratosis, acanthopapillomatosis, marked spongiosis and vacuolar interface dermatitis consistent with SDRIFE. (b) Gluteal biopsy showing orthokeratosis, acanthotic epidermis with spongiosis and an inflammatory infiltrate consistent with SDRIFE (hematoxylin-eosin stain, scale bar: 200 μm).

resulted in an unreasonable classification and undefined pathomechanism of the disease. In 2004, Häusermann et al. proposed the term SDRIFE to replace the broad and politically incorrect catchword "baboon syndrome". The term SDRIFE helps to differentiate this benign skin condition from drug eruptions such as AGEP, from drug rash with eosinophilia and systemic symptoms (DRESS), and from fixed drug eruptions.[5] The pathogenesis of SDRIFE is not yet completely understood. A delayed localized T-cell reaction has been suggested to trigger drug-induced allergic and toxic skin reactions. The fact that SDRIFE is caused by drugs without any existing sensitization clearly separates this condition from hematogenous contact dermatitis. Such T-cell activation, known as a "pharmacology interactions of drugs with immune receptors", however, may be related to the concentration or the dose of a drug. Yet, the reason why these reactions are site-specific remains unclear.[11,12] The areas of distribution are prone to mechanical friction, heat, and sweat. However, apocrine sweat glands are exclusively found in those exact areas. Those glands gain their function only after the introduction of sex hormones in puberty. The fact that there have not yet been any reported cases of SDRIFE in children might indicate that apocrine sweat glands are involved in the pathophysiology of the disease. More clinical studies will be necessary to help us understand the mechanisms behind this particular drug eruption.

It is still unclear how COVID-19 infections are connected to SDRIFE, but the number of SDRIFE cases has been increasing since the start of the pandemic in 2020.[12,13] Whether the virus itself, the broad immune response, or multimodal treatments including new antiviral agents have caused the rise in case numbers of SDRIFE or SDRIFE-like lesions remains unknown.[14,15]

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CONFLICT OF INTEREST STATEMENT

None.

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