

SDRIFE (Baboon Syndrome) Due to Paracetamol: Case Report

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SUMMARY The term “baboon syndrome” (BS) (recently known as symmetrical drug related intertriginous and flexural exanthema, SDRIFE) was introduced in 1984 to describe a specific skin eruption (resembling the red gluteal area of baboons) that occurred after systemic exposure to contact allergens. The crucial characteristics include a sharply defined symmetric erythema in the gluteal area and in the flexural or intertriginous folds without any systemic symptoms or signs. Because the term BS does not reflect the complete range of symptoms and is ethically problematic, it was replaced with a new term of SDRIFE. This term specifically refers to the distinctive clinical pattern of drug eruption induced by exposure to a systemically administered drug, presented as sharply demarcated symmetric erythematous areas of the gluteal/perianal area and/or V-shaped erythema of the inguinal/perigenital area (at least one other intertriginous/flexural localization) and absence of systemic symptoms and signs. We present a case of a 33-year-old man with SDRIFE due to Panadol® tablets (paracetamol). On admission, there was a densely disseminated, symmetric, livid to erythematous maculopapular exanthema present in both axillae, the sides of the trunk, inguinally spreading towards the thighs, in cubital and popliteal fossae, on the back sides of the upper legs, and in the gluteal regions. Awareness of SDRIFE (BS) as an unusual drug reaction is especially important since the connection between skin eruption and drug exposure may easily be overlooked or misdiagnosed.

KEY WORDS: SDRIFE, baboon syndrome, drug eruption, systemic contact dermatitis, paracetamol

INTRODUCTION

Drug reactions are often a difficult morphological diagnosis that usually presents itself as exanthema but can mimic a wide range of other skin conditions

(1-3). They usually involve type IV allergic reactions which, in sensitized patients, occur two to three days after initial exposure to the drug, while in non

sensitized patients they occur mostly after nine to ten days (sometimes up to two weeks after initial exposure) (1). Although drug eruptions can mimic a variety of skin diseases, they may rarely be similar to intertrigo and confined to specific, localized, well-demarcated areas, such as intertriginous regions (2,4).

Generally, the condition coined baboon syndrome (BS) was described as a special entity presenting as a mild, generalized cutaneous erythema appearing in intertriginous regions after oral exposure to either contact allergens (nickel, mercury, and other) or to certain drugs (5). Thus, the term BS was introduced to describe a specific dermatologic response, i.e. erythema of the buttocks and upper inner thighs resembling the red rump of baboons, occurring after systemic or local administration of contact allergens or certain drugs (6,7).

Historically, in 1983 Nakayama *et al.* published a report of 15 patients with sharply demarcated symmetric erythemas, predominantly on major flexural sites, which occurred after breaking a mercury thermometer (8). Afterwards, in 1984, Andersen *et al.* reported three patients with intertriginous and flexural erythemas (primarily involving the buttocks) that occurred after systemic administration or absorption of contact sensitizers (nickel, mercury and ampicillin) with the appearance similar to that of the red rump in baboons (6).

In 1994, Menne *et al.* proposed the term systemic contact dermatitis (SCD) for BS and other types of dermatitis (either with or without previous topical exposure) caused by systemic administration of substances including contact allergens and drugs (9). They also classified the disease as one of the five clinical reaction patterns (in addition to vesicular hand eczema, flexural dermatitis, maculopapular rash and vasculitis-like lesions) within the group of SCD without previous skin sensitization (9).

In 2003, Lachapelle *et al.* proposed the term allergic contact dermatitis syndrome (ACDS) to distinguish all clinical types of allergic contact dermatitis (ACD) (with previous skin sensitization) from other immune related contact reactions (without prior sensitization) and BS was considered as an example of ACDS (10). Therefore, BS was considered a variant within the spectrum of systemically induced ACD with a characteristic distribution.

Recently, it has been proposed to replace the term BS by the acronym SDRIFE (symmetrical drug-related intertriginous and flexural exanthema) for those reactions occurring after exposure to systemic drugs (5). The majority of cases of SDRIFE (BS) are caused by antibiotics (in particular beta-lactams) followed by

antihypertensives, radiocontrast media, chemotherapeutic agents, biologics and others (11). Thereby, the latency time between drug intake and onset of eruption ranges from a few hours to a few days. Therefore, the disease shows homogeneity for clinical distribution, range of primary cutaneous lesions, latency period after systemic absorption and course. On the other hand, SDRIFE shows heterogeneity in its histologic picture as well as in the results of skin tests and *in vitro* analysis (7). Histopathology is variable, with a reported predominance of superficial perivascular infiltrates, primarily composed of mononuclear cells, or in some cases neutrophils and eosinophils.

CASE REPORT

A 33-year-old male patient was admitted to our Department for diagnostic workup and treatment due to a densely disseminated maculopapular exanthema (Fig. 1). It was ascertained by history that the patient had noticed reddish papules in the left axilla 4 days prior to his admission, with the efflorescences spreading and becoming a maculopapular, symmetrically distributed rash involving axillary regions, sides of the trunk, inguinal regions, as well as cubital and popliteal fossae. There was also an intensive sensation of skin itching and burning. Before being



Figure 1. Skin changes in the patient.

admitted to our institution, the patient received on two occasions systemic corticosteroids (dexamethasone 4 mg, intramuscular administration, during two days) and oral antihistamines, with no significant improvement. There were, however, no accompanying systemic symptoms.

On admission, there was a densely disseminated, symmetric, livid to erythematous maculopapular exanthema present in both axillae, the sides of the trunk, inguinally and spreading towards the thighs, in cubital and popliteal fossae, on the back sides of the upper legs and in the gluteal regions. The rash was locally confluent to form areas of up to 30 cm in diameter.

We learned from the patient's medical history that, prior to the rash, the patient had been taking Panadol® tablets (paracetamol) for an upper respiratory tract infection (500 mg for only one day). According to the patient's statement, he has been previously using, on more than one occasion, paracetamol tablets from other drug manufacturers, which he had tolerated well, but this was the first time he took Panadol® tablets (paracetamol). The medication was discontinued immediately after dermatologic examination.

Diagnostic workup, including skin biopsy, was performed during hospitalization. Histopathologic analysis showed an intact epidermis on the surface, while in the dermis a moderately abundant, mononuclear and neutrophilic infiltrate around the capillaries was seen, with findings of mild exocytosis to the epidermis (Fig. 2). The histologic finding was in accordance with the clinical diagnosis of drug-induced exanthema of the SDRIFE (BS) type. Other laboratory tests were performed as well, with no major aberrations.

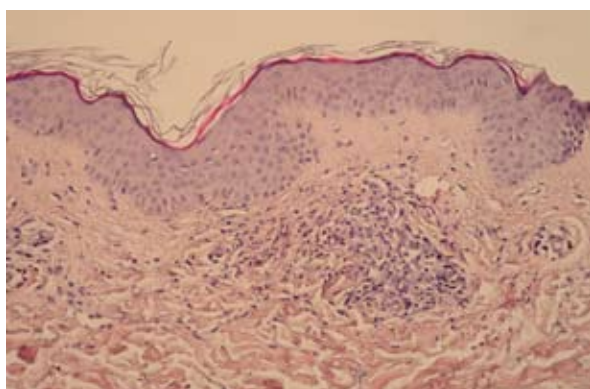


Figure 2. Histological analysis of skin lesions (HE; x200). The picture shows an intact epidermis on the surface, while in the dermis a moderately abundant, mononuclear and neutrophilic infiltrate around the capillaries was seen, with findings of mild exocytosis to the epidermis.

During hospital stay, oral corticosteroid (prednisone) was administered with gradual dose tapering, initially at a dose of 30 mg daily (for 5 days), followed by 20 mg daily (for 3 days), and finally 10 mg daily (for 2 days), as well as parenteral and oral antihistamines (after discharge, he continued taking antihistamine therapy). A topical corticosteroid (attenuated betamethasone cream) was also applied. The skin changes regressed completely within 10 days.

Then the patient was discharged from the hospital and advised to present to another hospital where specialized allergic testing (e.g., lymphocyte transformation test, drug provocation test, delayed intradermal test, patch test) for suspected drug (paracetamol) was available, since these tests could not be done at our hospital. However, the patient failed to do it. Yet, he was tested at our hospital to exclude other etiologic factors: allergy skin tests including prick tests to inhalant and nutritive allergens, food preservatives and additives; patch testing with the European Standard Series of allergens (according to the International Contact Dermatitis Research Group guidelines), and the results were negative.

DISCUSSION

SDRIFE (BS) is a disease that causes problems in recognition, terminology and etiopathogenesis ever since the first description of its clinical features. After the initial understanding of BS as a form of a hematogenous or systemic contact-type dermatitis (SCTD), the most recent term SDRIFE is being increasingly used (when referred to a drug reaction) (12-15). Thereby, the initial views of SDRIFE (BS) were based on the observation that the skin eruption was characterized by sharp, well-defined borders (as it is in contact dermatitis, indicating SCTD); positive patch test in most (although not all) cases, and a positive correlation between sensitivity to mercury/nickel and skin eruption following their oral ingestion (2,6,12,13). Although several of SDRIFE (BS) cases probably are manifestations of hematogenous SCTD (as a flare-up of an eruption at exactly the same site of a previous sensitization with the same allergen), it seems very unlikely that this mechanism underlies all or even most of the cases described (2,13). It is also important to emphasize that it is quite unlikely for medications such as penicillin and synthetic penicillins, cephalosporins, analgesics, chemotherapeutics and other drugs to be included in topical preparations or applied on the skin.

There is another more encompassing concept that the disease is the result of a recall phenomenon. According to this theory, SDRIFE (BS) represents a

recall of any form of dermatitis (unrelated to the drug currently in question) that occurred in the past in the same area as a new drug eruption. If this is the case, then the agent causing SDRIFE (BS) is generally different and unrelated to the agent that caused dermatitis in the past, even though it might be the same in specific cases (2).

Thereby, the acronym SDRIFE, standing for symmetric drug-related intertriginous and flexural exanthema, seems to be a reasonable term. Hausermann *et al.* (2004) have proposed 5 diagnostic criteria for SDRIFE: 1) exposure to a systemically administered drug either at the first or repeated dose (excluding contact allergens); 2) sharply demarcated erythema of the gluteal/perianal area and/or V-shaped erythema of the inguinal/perigenital area; 3) involvement of at least one other intertriginous/flexural localization; 4) symmetry of the affected areas; and 5) absence of systemic symptoms or signs (7).

Recently, abbreviations which can be easily remembered are trying to be used for practical reasons to describe specific drug eruptions, e.g., toxic epidermal necrolysis (TEN), acute generalized exanthematous pustulosis (AGEP), drug reaction with eosinophilia and systemic symptoms (DRESS) and fixed drug eruptions (FDE) (7,16,17). Thus, TEN is a potentially life-threatening dermatologic disorder characterized by widespread erythema, necrosis, and bullous detachment of the epidermis and mucous membranes, resulting in exfoliation and possible sepsis and/or death. AGEP is, thereby, a disseminated erythrodermic eruption with primarily non-follicular pustules associated with high fever and sometimes edema of the face with blood neutrophilia (17,18). DRESS involves maculopapular rashes, systemic symptoms, organ involvement, eosinophilia, and may be associated with potentially lethal organ involvement such as fulminant hepatitis (7,16,19). FDE includes development of asymmetric, erythematous, round-oval patches as a result of systemic exposure to a drug. We support the use of acronym SDRIFE (instead of BS) for several reasons. SDRIFE (unlike BS) is a neutral term that avoids ethically and culturally offensive comparison with an animal and distinguishes the disease as a relatively benign condition (in contrast to bullous eruptions or DRESS). Additionally, SDRIFE is characterized by a short latency period between drug intake and the onset of exanthema as well as the absence of systemic signs, as was the case in our patient (7). Other mentioned drug eruptions can only sometimes be similar to SDRIFE, having their own specificity.

Our case has shown the occurrence of SDRIFE in a patient who took Panadol® tablets (paracetamol),

which is a very rare occurrence. Namely, the majority of SDRIFE cases are caused by other groups of drugs, such as antibiotics (in particular beta-lactams), antihypertensives, radiocontrast media, chemotherapeutic agents, biologics, etc. According to literature review, there is only one similar case report of a 3-year-old boy presenting with sore throat, fever (lasting for two days) and rash on the face, buttocks and anogenital area, manifesting itself one day after the ingestion of cefadroxil, paracetamol and a cough-mixture (20). However, the boy took different drugs at the same time, therefore, it was difficult to claim that the exact etiologic agent was paracetamol, more presumably it was the antibiotic cefadroxil.

The precise immune and pathogenetic mechanisms of SDRIFE have yet to be elucidated, as well as the reason why some patients have a typical maculopapular exanthema, while others have urticaria, anaphylaxis, TEN, AGEP or SDRIFE (7). There is also insufficient evidence to propose additional predisposing factors for SDRIFE such as anatomical structures (e.g., the density of apocrine or eccrine glands (excretion of metabolized drugs), temperature, humidity or the recall phenomena). There is another explanation that the disease is a kind of recall phenomenon, with the characteristic localization and appearance of the eruption determined by an earlier bout of dermatitis. We support SDRIFE as a distinct subgroup of drug eruption entities with very specific involvement sites, presumably elicited by an allergic reaction of type IV (7).

Problems in diagnosis should also be mentioned. The diagnosis of SDRIFE is mostly based on the recognition of a clinical picture and history data on taking drugs (11). It has been shown, however, that there is no significant benefit in allergy testing. Outcomes of allergy tests are variable with positive delayed intradermal tests (reported for penicillin V, allopurinol); positive patch tests (for erythromycin, mitomycin, nystatin, pseudoephedrine); positive lymphocyte transformation tests (for erythromycin); and positive drug provocation tests (for clindamycin, cimetidine, corticosteroids, terbinafine, and valacyclovir). Unfortunately, outcomes of *in vivo* and *in vitro* tests have been inconsistent, and thus may not be useful in the identification of the putative drug (11). The possible reactions to the drug additives, which could be the case in our patient, should also be indicated. Therefore, the emerged skin changes could be induced by the reaction to other components or additives to the active ingredient (paracetamol).

CONCLUSION

We suggest that adverse drug reactions should always be considered on the differential diagnosis of intertriginous eruptions, especially in atypical and therapy-resistant cases. Awareness of SDRIFE (BS) as an unusual drug reaction is especially important since the connection between skin eruption and drug exposure may easily be overlooked or misdiagnosed.

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