

Co-occurrence of Symmetrical Drug-Related Intertriginous and Flexural Exanthema (SDRIFE) and Pigmented Fixed Drug Eruption (FDE) in a Single Patient Due to Doxycycline: A Case Report

Abstract

Symmetrical drug-related intertriginous and flexural exanthema (SDRIFE), and fixed drug eruption (FDE) are adverse cutaneous drug reactions. SDRIFE is most commonly associated with the use of beta-lactam antibiotics. There is only one case report describing SDRIFE due to intake of doxycycline in literature. Previously reported case describes the characteristic morphology of well-defined macular erythema over the flexural and intertriginous area. We here in report a 38-year-old male presented with unusual morphology of SDRIFE, and well circumscribed erythematous patches suggestive of FDE on the thigh and back after doxycycline intake. Histopathology was consistent with SDRIFE and FDE respectively. The skin lesions improved with 5 days of 40 mg oral prednisolone. After 6 weeks, drug provocation with doxycycline was done following which patient developed itching and erythema over the older sites. Though there is a single published report of SDRIFE due to doxycycline, our case had additional findings of having pigmented FDE lesions along with flexural lesions of SDRIFE.

Keywords: Baboon syndrome, doxycycline, drug eruption, drug hypersensitivity, fixed drug eruption, Symmetrical drug-related intertriginous and flexural exanthema

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Introduction

Symmetrical drug-related intertriginous and flexural exanthema (SDRIFE), previously called as baboon syndrome is characterized by erythema over the flexural and intertriginous areas with involvement of at least one large body folds. It is most commonly associated with the use of beta-lactam antibiotics.^[1] There was only one case report of doxycycline induced SDRIFE in literature. We are reporting a second case of doxycycline induced SDRIFE with additional pigmented FDE like lesions on thigh. In histopathology there were findings of both SDRIFE and FDE. Drug provocation test confirmed the diagnosis. Hence clinicians should be aware of the unusual side effect of Doxycycline.

Case Report

A 38-year-old male presented with symmetrical, ill to well-defined reddish patches, and blisters over flexures like axilla, sub mammary, inguinal and buttock area associated with pain and burning since

3 days. There was temporal correlation between onset of skin lesions and intake of doxycycline for the treatment of styne over his left eyelid. Within three to four hours of intake of doxycycline patient developed itching, and burning over flexural areas followed by appearance of erythematous patches and blisters. There was no similar episode in the past. On examination, there were symmetrically distributed, large ill to well defined areas of macular erythema with vesiculation, and bulla formation on surface over bilateral axilla, inner aspect of arms, sub mammary areas, inguinal areas, gluteal area and scrotum [Figure 1a and b]. In addition there were erythematous circular patches with bulla on surface over anterior thighs and back [Figure 1c]. Mucosae, palms and soles were completely free. Other systemic examinations were unremarkable. Histopathology from the lesion on axillary area revealed parakeratosis, irregular acanthosis with sub corneal bulla, perivascular inflammatory infiltrate and capillary congestion with RBC extravasation suggestive of SDRIFE [Figure 2a and b].

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From history, examination and histopathology diagnosis of SDRIFE due to doxycycline was made for flexural lesions. Similarly, histopathology from the thigh lesion revealed epidermal hyperkeratosis with apoptotic keratinocytes along with hydropic degeneration of basal cells with dermo epidermal bulla formation and pigment incontinence suggestive of FDE [Figure 3]. The patient was started with 40 mg prednisolone and within 5 days there was improvement of skin lesions with peeling and leaving hypopigmented areas. On follow-up after two months, the lesions over thighs had slate grey pigmentation suggestive of FDE whereas there was normal skin over flexures without any pigmentation [Figure 4a and b]. The patient was re admitted, informed consent was taken and was provoked with 1/4th dose of 100 mg oral doxycycline. After one hour of provocation there was site specific recurrence of the lesions in the form of marked erythema and itching over

both flexural areas and thighs [Figure 5a and b]. The Naranjo probability score was eight, suggesting a probable causal relationship between doxycycline and the eruption. The diagnosis of doxycycline induced SDRIFE and pigmented FDE was confirmed. Oral prednisolone 40 mg was started immediately and continued till symptom subsided. The patient was provided with a drug card certifying drug reaction due to doxycycline and was counselled to avoid doxycycline and chemically related drugs in future.

Discussion

SDRIFE is a cutaneous drug reaction characterized by symmetrical involvement of the flexural and intertriginous areas, occurring in the absence of systemic involvement.^[1] Diagnosis of SDRIFE is by temporal correlation of drug intake, well demarcated erythema over flexures and bilateral symmetrical involvement.^[2]

Similarly, FDE is a drug hypersensitive reaction that is characterised by well-defined dusky red painful patches that leave permanent deep post inflammatory hyperpigmentation. It is generally two types-pigmenting and non-pigmenting type.

The most common drug associated with SDRIFE is beta-lactam antibiotics, particularly amoxicillin.^[2] Other medications reported are anti hypertensives, radiocontrast media, monoclonal antibodies, fluconazole and itraconazole.



Figure 1: (a) Macular erythematous patches with vesicles and bulla over flexures. (b) Erythematous patches with blistering over axilla. (c) Well defined erythematous patch with bulla over thigh

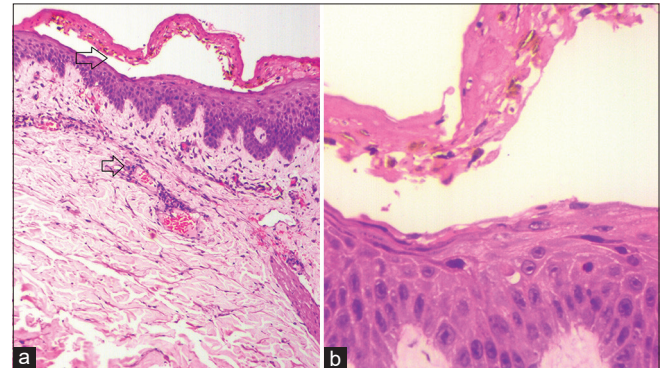


Figure 2: (a) Sub corneal cleft with perivascular inflammatory infiltrate from axilla (H and E x100). (b) High power view of sub corneal cleft (H and E x400)

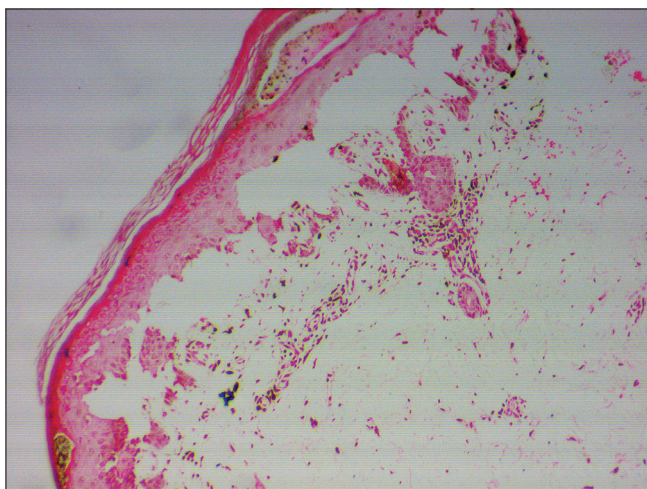


Figure 3: Sub epidermal cleft and melanin incontinence suggestive of FDE from thigh (H and E x100)



Figure 4: (a) Healing of flexural lesions with hypopigmentation. (b) Healing of FDE lesions with hyperpigmentation

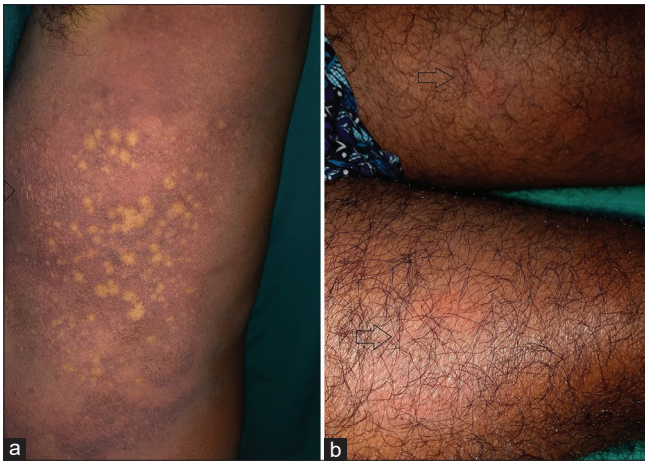


Figure 5: Site specific re-occurrence of erythema after drug provocation. (a) over flexural area (b) on prior FDE lesion on thigh

There was only one case report of SDRIFE induced by doxycycline by David *et al.*^[3] Skin findings in SDRIFE is previously described as symmetrical erythema over flexural areas. Sometimes skin showed tiny papules, pustules, vesicles and rarely bullae.^[4]

The mechanism of SDRIFE is unknown but is hypothesized to be due to a delayed hypersensitivity response resulting in a cutaneous eruption days after exposure to the drug.^[5] Skin biopsies from SDRIFE patients typically reveal a superficial perivascular infiltrate of inflammatory cells (commonly lymphocytes or eosinophils), with immunohistological studies demonstrating an infiltration of CD3+ and CD4+ T cells. These features suggest that SDRIFE shares a similar disease mechanism to type IV hypersensitivity reactions.^[5] Systemic provocation is still the criterion standard for diagnosis.

A rare non-pigmenting form was described as a distinctive reaction pattern with usually symmetrical, large, erythematous lesions on the buttocks and the major flexural and intertriginous areas,^[6] suggesting SDRIFE. Hence SDRIFE and FDE suggest different reactions in a spectrum. On literature search we could find a case report of both SDRIFE and FDE to amoxicillin in a paediatric patient.^[7]

Depending on the predominant type of drug-specific memory T-cells and the released cytokines that would determine the clinical phenotype of the drug eruption.^[8] In most reactions, different type IV reactions may occur together, and cytotoxic functions by CD4+ or CD8+ T cells (type IVc) seem to participate in all type IV reactions.^[8] It has been suggested that a combination of type IVa and IVc reaction is involved in SDRIFE, and type IVc reaction in FDE, hence suggesting coexistence or overlap of features in drug reactions.^[9] This could be the cause of unusual morphology and few FDE like lesions in the same patient.

Our case is unique in the sense this is the second reported case of SDRIFE due to doxycycline. Considering the widespread use of doxycycline, clinicians should be aware of this adverse effect. Again this was a challenging case with overlapping features of SDRIFE and FDE, suggesting that different drug-specific memory T-cells and related effector mechanisms (type IVa and IVc hypersensitivity reactions) might have acted simultaneously in the same patient. Authors suggest the overlapping features of different drug eruptions, because of their cytokine pathway overlap.

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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