Lenalidomide-induced symmetrical drug-related intertriginous and flexural exanthema

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Abstract

Symmetric drug-related intertriginous and flexural exanthema (SDRIFE) is a cutaneous drug reaction that presents with symmetrical erythema in the flexures. The reaction typically appears hours-to-days after drug exposure but has been reported to occur months after drug initiation. Diagnostic criteria include cutaneous reaction after exposure to a systemic drug, erythema of the gluteal region and/or V-shaped erythema of the inguinal areas, involvement of an additional intertriginous site, symmetry, and absence of systemic involvement. The rash typically presents as macular erythema. However, variations in morphology have been reported including papules, pustules, vesicles, and bullae. The histopathology of SDRIFE is non-specific and the diagnosis is made clinically. Cessation of the causative drug leads to gradual rash resolution. Beta-lactam antibiotics are the most implicated medications but case reports describe SDRIFE following monoclonal antibodies, chemotherapeutic agents, and various other medications. We present a patient with SDRIFE secondary to lenalidomide, an immunomodulatory agent. This case highlights the importance of considering SDRIFE in the differential diagnosis of patients presenting with intertriginous erythema.

Keywords: baboon syndrome, drug eruption, lenalidomide, multiple myeloma, SDRIFE

Introduction

Symmetrical drug-related intertriginous and flexural exanthema (SDRIFE) is an immune-mediated type IV hypersensitivity reaction that occurs after systemic administration of the culprit medication. In 1984, SDRIFE was initially described as "baboon syndrome" because the rash resembled the red rump of baboons due to its distribution on the buttocks and inner thighs [1]. In 2004, Hausermann coined the term SDRIFE as a more appropriate name for the cutaneous reaction [2].

The diagnostic criteria for SDRIFE include: 1) cutaneous reaction after exposure to a systemic medication after the first or repeated doses; 2) well-demarcated erythema of the gluteal/perianal area and/or V-shaped erythema of the inguinal area; 3) involvement of at least one other intertriginous or flexural fold; 4) symmetrical distribution in the affected regions; and 5) absence of systemic involvement [3]. The rash typically presents as macular erythema, but variations in morphology have been reported including papules, pustules, vesicles, and bullae. The histological features of SDRIFE include superficial perivascular infiltrate of mononuclear cells [2]. In some instances, eosinophils and neutrophils can also be noted [2]. Thus, the histology of SDRIFE is non-specific, making it a clinical diagnosis.

Although the clinical course is self-limited upon cessation of the culprit drug, it can progress to a generalized exanthematous eruption with continued exposure to the medication. Beta-lactam antibiotics, especially amoxicillin, is the most common cause of SDRIFE. It has also been reported in association with other antibiotics, antihypertensives, non-steroidal anti-inflammatory drugs, chemotherapeutics, and monoclonal

antibodies [2]. We report a case of SDRIFE caused by lenalidomide.

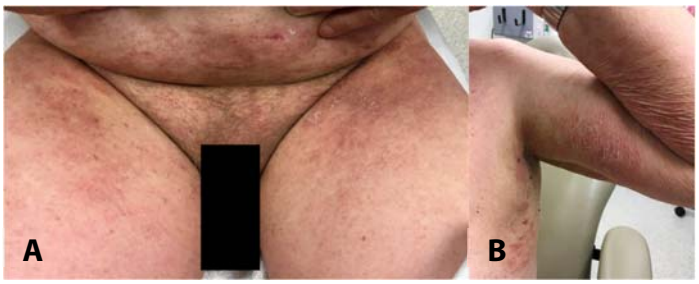

Figure 1. ***A)*** *Symmetric erythematous patches on the upper inner thighs and lower pannus.* ***B)*** *Digitate erythematous patches on the axilla.*

Case Synopsis

An 80-year-old man with multiple myeloma was referred to the dermatology clinic for evaluation of a rash in the intertriginous areas. He was considered to have an "yeast infection" and was using topical miconazole compounded with betamethasone. The patient had been treated with lenalidomide for two years. He developed a similar rash three months earlier that resolved upon discontinuation of lenalidomide. He was restarted on the lenalidomide and developed the same rash about 10 days after rechallenge. Examination revealed symmetric, scaly erythematous patches involving the walls of the axillae, bilateral dorsal forearms, bilateral inner thighs, and lower pannus (**Figure 1**). KOH preparation was negative for fungal and yeast elements.

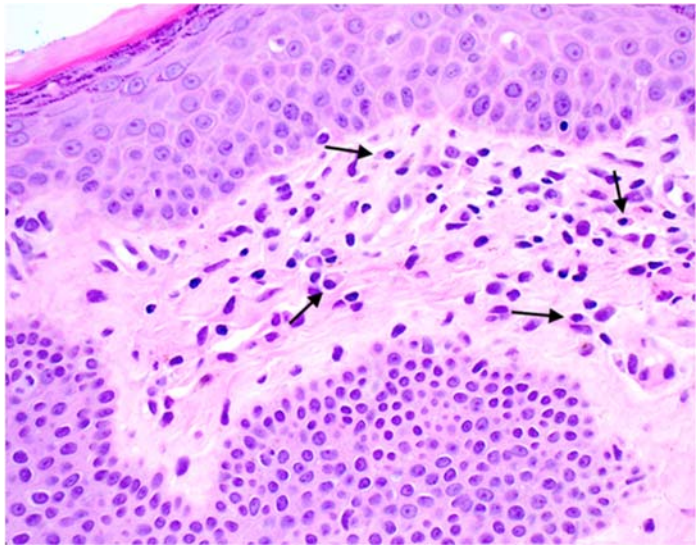

Figure 2. *Dermal plasma cells (arrows) and lymphocytes noted on punch biopsy.*

A punch biopsy revealed chronic dermatitis with dermal plasma cells (**Figure 2**). In-situ hybridization for kappa and lambda light chains did not demonstrate monoclonality but showed a normal kappa to lambda ratio of 2:1. The patient did not report any systemic symptoms. Lenalidomide was discontinued and he had significant improvement of his rash within 24 hours of discontinuation. Given the timeline, symptoms, non-specific histology, and complete resolution of symptoms with cessation of lenalidomide, the patient was diagnosed with SDRIFE.

Case Discussion

The pathogenesis of SDRIFE is not well understood, but it is believed to be a systemic allergic dermatitis [3]. Although SDRIFE is rare, it is most commonly associated with beta-lactam antibiotics. However, other non-beta-lactam antibiotics, such as clindamycin and trimethoprim/sulfamethoxazole, have been associated with SDRIFE [2]. SDRIFE has also been reported to develop following the administration of codeine, pseudoephedrine, allopurinol, heparin, hydroxyurea, oxycodone, naproxen, risperidone, antihypertensives, chemotherapeutic agents such as enfortumab vedotin, and monoclonal antibodies such as infliximab [2, 4].

We present a case of lenalidomide-induced SDRIFE. We used the adverse drug reaction probability scale developed by Naranjo et al. in 1981 to establish causality between lenalidomide and SDRIFE (**Table 1**). Our case scored eight points; a total score greater than nine indicates definite relationship, five to eight indicates probable relationship, one to four indicates possible relationship, and less than or equal to zero indicates doubtful relationship [5]. Lenalidomide is frequently used for the treatment of multiple myeloma and has been associated with severe cutaneous adverse events.

Lenalidomide is an immunomodulatory agent used to treat multiple myeloma and myelodysplastic

Table 1. *Naranjo et al. adverse drug reaction scale with numbers in bold highlighting the score for this patient's clinical case [5].*

	Yes	No	Do not know	Score
Are there previous conclusive reports on this reaction?	+1	**0**	0	0
Did the adverse event appear after the suspected drug was administered?	**+2**	-1	0	+2
Did the adverse reaction improve when the drug was discontinued or a specific antagonist was administered?	**+1**	0	0	+1
Did the adverse reaction reappear when the drug was readministered?	**+2**	-1	0	+2
Are there alternative causes (other than the drug) that could on their own have caused the reaction?	-1	**+2**	0	+2
Did the reaction reappear when a placebo was given?	-1	+1	**0**	0
Was the drug detected in the blood (or other fluids) in concentrations known to be toxic?	+1	0	**0**	0
Was the reaction more severe when the dose was increased, or less severe when the dose was decreased?	+1	0	**0**	0
Did the patient have a similar reaction to the same or similar drugs in any previous exposure?	+1	**0**	0	0
Was the adverse event confirmed by any objective evidence?	**+1**	0	0	+1
Total Score				8

syndrome. Although its mechanism of action is unclear, it has anti-inflammatory, immunomodulatory, anti-proliferative, anti-neoplastic, and anti-angiogenic therapeutic properties [6]. The most commonly reported adverse effects of lenalidomide include thrombocytopenia, neutropenia, and gastrointestinal problems [6,7]. In a retrospective study, cutaneous adverse effects were noted in 29% of multiple myeloma patients treated with lenalidomide [8]. In 72% of these patients, these cutaneous reactions were noted within the first month of initiation of therapy [8]. Reported cutaneous adverse events associated with lenalidomide include morbilliform, urticarial, purpuric, granulomatous, and acneiform eruptions [7]. Severe cutaneous reactions include Stevens-Johnson syndrome, erythema multiforme, and toxic epidermal necrolysis [7]. To date, there have been no associations between lenalidomide and SDRIFE.

Conclusion

We present a case of SDRIFE caused by lenalidomide. This case highlights the importance of considering SDRIFE in the differential diagnosis of intertriginous eruptions. Clinicians should be aware of the association of SDRIFE with lenalidomide to help avoid misdiagnosis.

Potential conflicts of interest

The authors declare no conflicts of interest.

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