To the Editor:

Symmetric drug-related intertriginous and flexural exanthema (SDRIFE) is a curious disorder that has undergone many clinical transformations since first being described by Andersen et al.1 in 1984 using the term baboon syndrome. Initially described as a mercury hypersensitivity reaction resulting in an eruption resembling the red-bottomed baboon, this exanthema has expanded in definition with inciting agents, clinical features, and diagnostic criteria. Its prognosis, however, has remained stable and favorable throughout the decades. The condition is almost universally benign and self-limited.1-3 As new cases are reported in the literature and the paradigm of SDRIFE continues to shift, its prognosis also may warrant reconsideration and respect as it may have devastating potential.

A 39-year-old woman who was otherwise healthy presented to the emergency department after developing a rapidly evolving and blistering rash on the left flank. Hours later, the rash had progressed to a sharply demarcated, confluent, erythematous plaque with central ulceration and large flaccid bullae peripherally, encompassing 16% of the total body surface area and extending from the gluteal cleft to the tip of the scapula along the left flank (Figure 1) with no vaginal or mucosal involvement. The patient recently had completed a 10-day course of amoxicillin–clavulanic acid 2 days prior for a cat bite on the right dorsal wrist. Additional history confirmed the absence of prodromal fever, fatigue, or chills. Inciting trauma including chemical and thermal burns was denied. Potential underlying psychosocial confounders were explored and were unrevealing.

Laboratory test results including a complete blood cell count and metabolic panel as well as vital signs were unremarkable except for slight leukocytosis at 14,000/µL (reference range 4500–11,000/µL). A punch biopsy taken from the patient’s left upper back at the time of admission revealed a sparse, superficial, perivascular infiltrate of lymphocytes and rare neutrophils with a largely absent epidermis and an occasional focal necrosis of adnexal epithelium (Figure 2). Immunofluorescence was negative for specific deposition of IgG, IgA, IgM, C3, or fibrinogen. Wound culture also returned negative, and the Naranjo adverse drug reaction probability scale score was calculated to be 4 out of 12, indicating a possible adverse drug reaction.4

Given the extent and distribution of the rash as well as the full-thickness dermal involvement, the patient was transferred to the burn unit for subsequent care. At
8-month follow-up, she experienced severe, symptomatic, hypertrophic scarring and was awaiting intralesional triamcinolone acetonide injections. The patient subsequently was lost to follow-up.

The clinical picture of SDRIFE has remained obscure over the last 30 years, likely owing to its rarity and unclear pathogenesis. Diagnostic criteria for SDRIFE were first proposed by Häusermann et al in 2004 and contained 5 elements: (1) occurrence after (re)exposure to systemic drugs, (2) sharply demarcated erythema of the gluteal region or V-shaped erythema of the inguinal area, (3) involvement of at least 1 other intertriginous location, (4) symmetry of affected areas, and (5) absence of systemic symptoms and signs. Based on these clinical criteria, our patient fulfilled 3 of 5 elements, with deductions for symmetry of affected areas and involvement of other intertriginous locations. Histopathologic findings in SDRIFE predominantly are nonspecific with superficial perivascular mononuclear infiltrates; however, prior reports have confirmed the potential for vacuolar changes and hydropic degeneration in the basal cell layer with subepidermal bullae formation. Similarly, the presence of bullae has been described, though they are somewhat atypical in SDRIFE. Taken together, we speculate that these findings may support a diagnosis of SDRIFE with atypical presentation in our patient, though an alternative diagnosis of bullous fixed drug eruption (FDE) could not be ruled out.

Historically, SDRIFE has been associated with a benign course. The condition typically arises within a few hours to
days following administration of the offending agent, most commonly amoxicillin or another β-lactam antibiotic.1 Most cases spontaneously resolve via desquamation within 1 to 2 weeks. We present an unusual case of amoxicillin-induced full-thickness epidermal necrosis resulting in symptomatic sequelae, which exhibited findings of SDRIFE, bullous FDE, or Stevens-Johnson syndrome/toxic epidermal necrolysis, suggesting the possibility for a common pathway underlying the pathogenesis of these conditions.

The diagnostic uncertainty that commonly accompanies these various toxic drug reactions may in part relate to their underlying immunopathogenesis. Although the exact mechanism by which SDRIFE results in its characteristic skin lesions has not been fully elucidated, prior work through patch testing, lymphocyte transformation assays, and immunohistochemical staining of biopsies has suggested a type IV delayed hypersensitivity (DTH) reaction.7-10 Specifically, SDRIFE appears to share features of both DTH type IVa—involving CD4+ helper T cells (T_{H1}), monocytes, and IFN-γ signaling—and DTH type IVc—involving cytotoxic CD4 and CD8 cells, granzyme B action, and FasL signaling.11,12 A similar inflammatory milieu has been implicated in numerous toxic drug eruptions, including Stevens-Johnson syndrome/toxic epidermal necrolysis and FDE.11,13 This mechanistic overlap may explain the overlap seen clinically among such conditions.

In the undifferentiated patient, categorization of the clinical syndrome proves helpful in prognostication and therapeutic approach. The complexities and commonalities intrinsic to these syndromes, however, may simultaneously preclude certain cases from neatly following the predefined rules. These atypical presentations, while diagnostically challenging, can in turn offer a unique opportunity to reexamine the current state of disease understanding to better allow for appropriate classification.

Despite its rarity, SDRIFE should be considered in the differential of undiagnosed drug eruptions, particularly as new clinical presentations emerge. Careful documentation and timely declaration of future cases will prove invaluable for diagnostic and therapeutic advancements should this once-benign condition develop a more destructive potential.

REFERENCES