Generalized Fixed Drug Eruptions Require Urgent Care: A Case Series

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PRACTICE **POINTS**

- Although localized fixed drug eruption (FDE) is a relatively benign diagnosis, generalized bullous FDE requires urgent management and may necessitate intensive burn care.
- Patients with lupus are at increased risk for drug eruptions due to polypharmacy, and there is a wide differential for bullous eruptions in these patients.

A generalized fixed drug eruption (FDE) is an uncommon but potentially dangerous reaction to medication. In this case series, we present 1 patient with a generalized FDE and 2 patients with generalized bullous FDE that resolved with cyclosporine, though 1 patient required close monitoring in the intensive care unit. Immediate acceleration of care upon development and recognition of generalized bullous FDE is essential, as the mortality rate is similar to Stevens-Johnson syndrome (SJS)/toxic epidermal necrolysis (TEN).

Recognizing cutaneous drug eruptions is important for treatment and prevention of recurrence. Fixed drug eruptions (FDEs) typically are harmless but can have major negative cosmetic consequences for patients. In its more severe forms, patients are at risk for widespread epithelial necrosis with accompanying complications. We report 1 patient with generalized FDE and 2 with generalized bullous FDE. We also discuss the recognition and treatment of the condition. Two patients previously had been diagnosed with systemic lupus erythematosus (SLE).

Case Series

Patient 1—A 60-year-old woman presented to dermatology with a rash on the trunk and groin folds of 4 days' duration. She had a history of SLE and cutaneous lupus treated with hydroxychloroquine 200 mg twice daily and topical corticosteroids. She had started sulfamethoxazole-trimethoprim for a urinary tract infection with a rash appearing 1 day later. She reported burning skin pain with progression to blisters that "sloughed" off. She denied any known history of allergy to sulfa drugs. Prior to evaluation by dermatology, she visited an urgent care facility and was prescribed hydroxyzine and intramuscular corticosteroids. At presentation to dermatology 3 days after taking sulfamethoxazole-trimethoprim, she had annular flaccid bullae and superficial erosions with dusky borders on the right posterior thigh, right side of the chest, left inframammary fold, and right inguinal fold (Figure 1). She had no ocular, oral, or vaginal erosions. A diagnosis of generalized bullous FDE was favored over erythema multiforme or Stevens-Johnson syndrome (SJS)/toxic epidermal necrolysis (TEN). Shave biopsies from lesions on the right posterior thigh and right inguinal fold demonstrated interface dermatitis with epidermal necrosis, pigment incontinence, and numerous eosinophils. Direct immunofluorescence of the perilesional skin was negative

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for immunoprotein deposition. These findings were consistent with the clinical impression of generalized bullous FDE. Prior to receiving the histopathology report, the patient was initiated on a regimen of cyclosporine 5 mg/kg/d in the setting of normal renal function and followed until the eruption resolved completely. Cyclosporine was tapered at 2 weeks and discontinued at 3 weeks.

Patient 2—A 32-year-old woman presented for follow-up management of discoid lupus erythematosus. She had a history of systemic and cutaneous lupus, juvenile rheumatoid arthritis, and mixed connective tissue disease managed with prednisone, hydroxychloroquine, azathioprine, and belimumab. Physical examination revealed scarring alopecia with dyspigmentation and active inflammation consistent with uncontrolled cutaneous lupus. However, she also had oval-shaped hyperpigmented patches over the left breast, clavicle, and anterior chest consistent with a generalized FDE (Figure 2). The patient did not recall a history of similar lesions and could not identify a possible trigger. She was counseled on possible culprits and advised to avoid unnecessary medications. She had an unremarkable clinical course; therefore, no further intervention was necessary.

Patient 3—A 33-year-old man presented to the emergency department with a painful rash on the chest and back of 2 days' duration that began 1 hour after taking naproxen (dosage unknown) for back pain. He had no notable medical history. The patient stated that the rash had slowly worsened and started to develop blisters. He visited an urgent care facility 1 day prior to the current presentation and was started on a 5-day course of prednisone 40 mg daily; the first 2 doses did not help. He denied any mucosal involvement apart from a tender lesion on the penis. He reported a history of an allergic reaction to penicillin. Physical examination revealed extensive dusky violaceous annular plaques with erythematous borders across the anterior and posterior trunk (Figure 3). Multiple flaccid bullae developed within these plaques, involving 15% of the body surface area. He was diagnosed with generalized bullous FDE based on the clinical history and histopathology. He was admitted to the burn intensive care unit and treated with cyclosporine 3 mg/kg/d with subsequent resolution of the eruption.

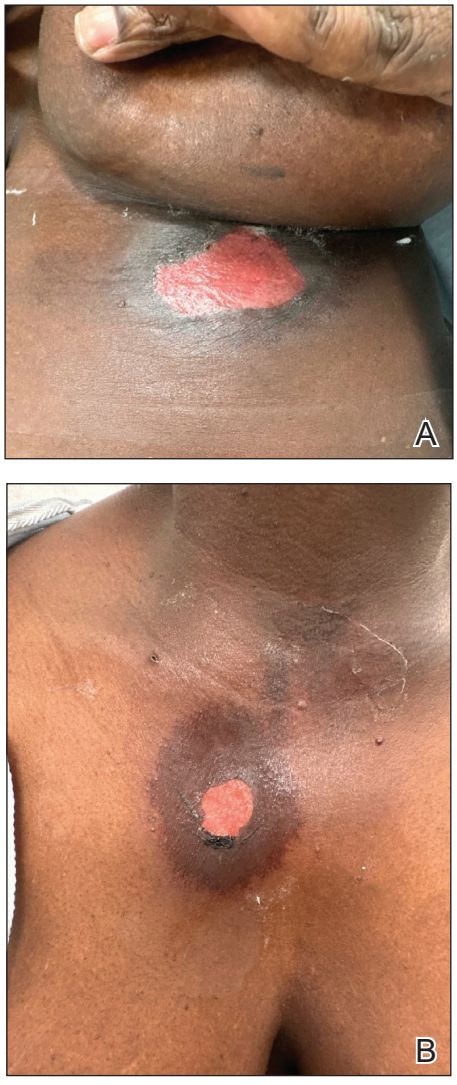

FIGURE 1. A and B, Eroded bullae on annular hyperpigmented plaques of the left inframammary fold and right side of the chest, respectively, in a patient with a generalized bullous fixed drug eruption (patient 1).

Comment

Presentation of FDEs—A fixed drug eruption manifests with 1 or more well-demarcated, red or violaceous, annular patches that resolve with postinflammatory hyperpigmentation; it occasionally may manifest with bullae. Initial

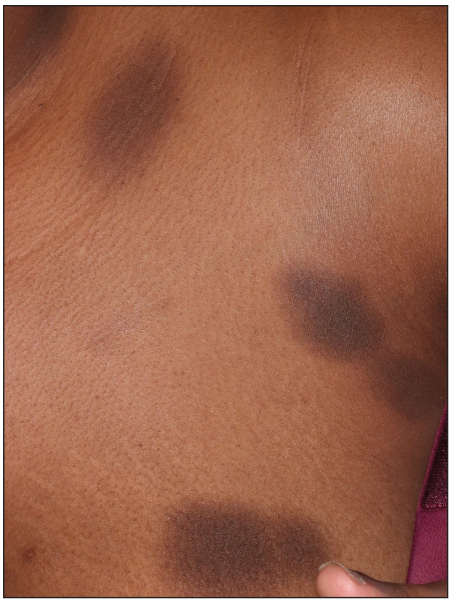

FIGURE 2. Hyperpigmented patches were noted on the left side of the chest in a patient with a generalized fixed drug eruption (patient 2).

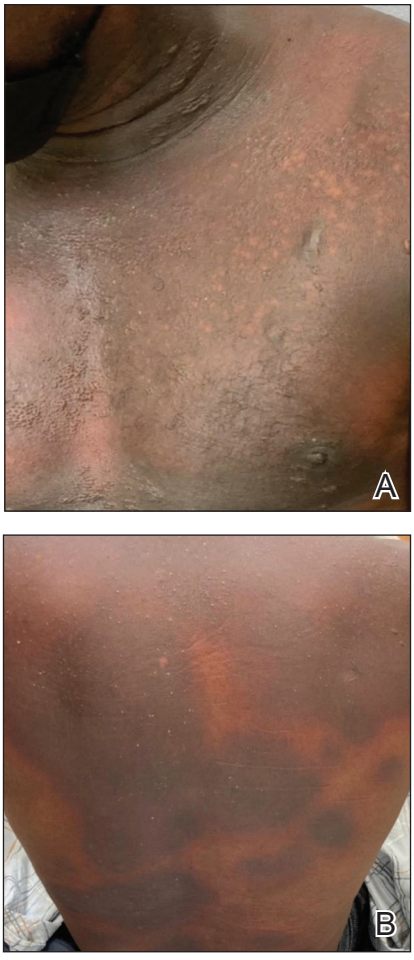

FIGURE 3. A, Erythematous patches were scattered across the chest with focal, intact, flaccid bullae in a patient with a generalized bullous fixed drug eruption (patient 3). B, Large confluent annular hyperpigmented, dusky patches with erythematous rims and several bullae were scattered across the back.

eruptions may occur up to 2 weeks following medication exposure, but recurrent eruptions usually happen within minutes to hours later. They often are in the same location as prior lesions. A fixed drug eruption can be solitary, scattered, or generalized; a generalized FDE typically demonstrates multiple bilateral lesions that may itch, burn, or cause no symptoms. Patients can experience an FDE at any age, though the median age is reported as 35 to 60 years of age.[1] A fixed drug eruption usually occurs after ingestion of oral medications, though there have been a few reports with iodinated contrast.[2] Well-known culprits include antibiotics (eg, sulfamethoxazole-trimethoprim, tetracyclines, penicillins/cephalosporins, quinolones, dapsone), nonsteroidal anti-inflammatory drugs, acetaminophen (eg, paracetamol), barbiturates, antimalarials, and anticonvulsants. It also can occur with vaccines or with certain foods (fixed food eruption).[3,4] Clinicians may try an oral drug challenge to identify the cause of an FDE, but in patients with a history of a generalized FDE, the risk for developing an increasingly severe reaction with repeated exposure to the medication is too high.[5]

Histopathology—Patch testing at the site of prior eruption with suspected drug culprits may be useful.[6] Histopathology of FDE typically demonstrates vacuolar changes at the dermoepidermal junction with a lichenoid lymphocytic infiltrate. Early lesions often show a predominance of eosinophils. Subepidermal clefting is a feature of the bullous variant. In an active lesion, there are large numbers of CD8+ T lymphocytes expressing natural killer cell–associated molecules.[7] The pathologic mechanism is not well understood, though it has been hypothesized that memory CD8+ cells are maintained in specific regions of the epidermis by IL-15 produced in the microenvironment and are activated upon rechallenge.[7]

Considerations in Generalized Bullous FDE—Generalized FDE is defined in the literature as an FDE with involvement of 3 of 6 body areas: head, neck, trunk, upper limbs, lower limbs, and genital area. It may cover more or less than 10% of the body surface area.[8-10] Although an isolated FDE frequently is asymptomatic and may not be cause for alarm, recurring drug eruptions increase the risk for development of generalized bullous FDE. Generalized bullous FDE is a rare subset. It is frequently misdiagnosed, and data on its incidence are uncertain.[11] Of note, several pathologies causing bullous lesions may be in the differential diagnosis, including bullous pemphigoid; pemphigus vulgaris; bullous SLE; or bullae from cutaneous lupus, staphylococcal scalded skin syndrome, erythema multiforme, or SJS/TEN.[12] When matched for body surface area involvement with SJS/TEN, generalized bullous FDE shares nearly identical mortality rates[10]; therefore, these patients should be treated with the same level of urgency and admitted to a critical care or burn unit, as they are at serious risk for infection and other complications.[13]

Clinical history and presentation along with histopathologic findings help to narrow down the differential diagnosis. Clinically, generalized bullous FDE does not affect the surrounding skin and manifests sooner after drug exposure (1–24 hours) with less mucosal involvement than SJS/TEN.[9] Additionally, SJS/TEN patients frequently have generalized malaise and/or fever, while generalized bullous FDE patients do not. Finally, patients with generalized bullous FDE may report a history of a cutaneous eruption similar in morphology or in the same location.

Histopathologically, generalized bullous FDE may be similar to FDE with the addition of a subepidermal blister. Generalized bullous FDE patients have greater eosinophil infiltration and dermal melanophages than patients with SJS/TEN.[9] Cellular infiltrates in generalized bullous FDE include more dermal CD41 cells, such as Foxp31 regulatory T cells; fewer intraepidermal CD561 cells; and fewer intraepidermal cells with granulysin.[9] Occasionally, generalized bullous FDE causes full-thickness necrosis. In those cases, generalized bullous FDE cannot reliably be distinguished from other conditions with epidermal necrolysis on histopathology.[13]

FDE Diagnostics—A cytotoxin produced by cytotoxic T lymphocytes, granulysin can be measured to aid in diagnosis of FDE, though this test may not be widely available. High levels of granulysin in the blister fluid and serum can be used to distinguish SJS/TEN, erythema multiforme, and localized and generalized bullous FDE from other non–cytotoxic T lymphocyte–mediated bullous skin disorders, such as bullous pemphigoid, pemphigus, and bullous SLE.[14] Blister granulysin levels are notably lower in generalized bullous FDE than in SJS/TEN.[9,14] Chen et al[14] also found that granulysin levels can be used to gauge disease progression given that the levels sharply decrease after patients have reached maximal skin detachment.

Management—Avoidance of the inciting drug often is sufficient for patients with an FDE, as demonstrated in patient 2 in our case series. Clinicians also should counsel patients on avoidance of potential cross-reacting drugs. Symptomatic treatment for itch or pain is appropriate and may include antihistamines or topical steroids. Nonsteroidal anti-inflammatory drugs may exacerbate or be causative of FDE. For generalized bullous FDE, cyclosporine is favored in the literature[15,16] and was used to successfully treat both patients 1 and 3 in our case series. A short course of systemic corticosteroids or intravenous immunoglobulin also may be considered. Mild cases of generalized bullous FDE may be treated with close outpatient follow-up (patient 1), while severe cases require inpatient or even critical care monitoring with aggressive medical management to prevent the progression of skin desquamation (patient 3). Patients with severe oral lesions may require inpatient support for fluid maintenance.

Lupus History—Two patients in our case series had a history of lupus. Lupus itself can cause primary bullous lesions. Similar to FDE, bullous SLE can involve sun-exposed and nonexposed areas of the skin as well as the mucous membranes with a predilection for the lower vermilion lip.[17] In bullous SLE, tense subepidermal blisters with a neutrophil-rich infiltrate form due to circulating antibodies to type VII collagen. These blisters have an erythematous or urticated base, most commonly on the face, upper trunk, and proximal extremities.[18] In both SLE with skin manifestations and lupus limited to the skin, bullae may form due to extensive vacuolar degeneration. Similar to TEN, they can form rapidly in a widespread distribution.[17] However, there is limited mucosal involvement, no clear drug association, and a better prognosis. Bullae caused by lupus will frequently demonstrate deposition of immunoproteins IgG, IgM, IgA, and complement component 3 at the basement membrane zone in perilesional skin on direct immunofluorescence. However, negative direct immunofluorescence does not rule out lupus.[12] At the same time, patients with lupus frequently have comorbidities requiring multiple medications; the need for these medications may predispose patients to higher rates of cutaneous drug eruptions.[19] To our knowledge, there is no known association between FDE and lupus.

Conclusion

Patients with acute eruptions following the initiation of a new prescription or over-the-counter medication require urgent evaluation. Generalized bullous FDE requires timely diagnosis and intervention. Patients with lupus have an increased risk for cutaneous drug eruptions due to polypharmacy. Further investigation is necessary to determine if there is a pathophysiologic mechanism responsible for the development of FDE in lupus patients.

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