

Drug Hypersensitivity Reactions Presenting as a Morbilliform Eruption With Islands of Sparing

To the Editor:

Cutaneous adverse drug reactions are common in hospitalized patients and contribute to patient morbidity, prolonged hospital stays, and the rising cost of health-care.^{1,3} In the hospitalized patient with a drug eruption and an extensive medication list, identifying the culpable drug often is a challenging task.^{4,5} Physicians relying on clinical and histopathological clues must recognize a wide range of clinicopathologic entities that comprise cutaneous manifestations of drug reactions. Well-described patterns include morbilliform, urticarial, papulosquamous, lichenoid, bullous, erosive, pustular, eczematous, and fixed drug eruptions.⁶ Two cases of cephalosporin-induced drug eruptions manifesting as widespread morbilliform eruptions with islands of sparing and histologic evidence of spongiotic dermatitis on skin biopsy were diagnosed at the Columbia University Medical Center (CUMC), New York, New York.

Case Reports

Patient 1—A 77-year-old man was admitted to CUMC following a ruptured arteriovenous malformation. His course was complicated by hospital-acquired pneumonia for which cefepime was initiated. The dermatology department was consulted 11 days later for a new diffuse symmetric morbilliform eruption. On examination, clearly delineated unaffected areas, islands of sparing, were seen within otherwise confluent widespread erythema (Figure 1). The palms, soles, and mucous membranes were spared. Hematology profile, renal function, and hepatic function tests did not reveal any abnormalities. Skin biopsy of the left thigh demonstrated spongiotic dermatitis with a predominantly mononuclear cell perivascular dermal infiltrate (Figure 2). After discontinuation of cefepime, the rash gradually resolved within a few weeks.

Patient 2—An 84-year-old man was admitted to CUMC following a myocardial infarction. Coronary artery bypass grafting was complicated by respiratory distress that required intubation and transfer to the intensive care unit where a plethora of medications were started including ceftriaxone, esomeprazole, meropenem, and piperacillin-tazobactam. The

dermatology department was consulted 6 days later to evaluate a slowly evolving, symmetric, diffuse morbilliform eruption that had acutely worsened following the administration of cefepime. Islands of sparing were seen within otherwise confluent widespread erythema. The face, palms, soles, and mucous membranes were unaffected. Laboratory studies revealed



Figure 1. Discrete islands of sparing within otherwise confluent erythema on the abdomen.

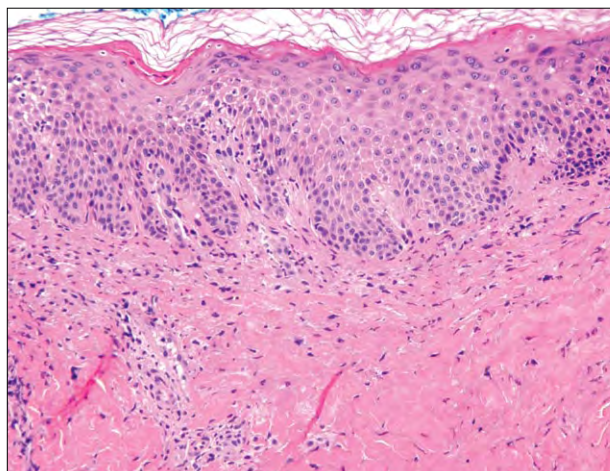


Figure 2. Skin biopsy of an erythematous patch on the left thigh showed epidermal spongiotic dermatitis with a predominantly mononuclear cell perivascular dermal infiltrate (H&E, original magnification $\times 20$).

leukocytosis (white blood cell count, $22.9 \times 10^9/L$ [reference range, $4.5\text{--}11.0 \times 10^9/L$] with 5% eosinophils [reference range, 2.7%]) and a serum creatinine level of 1.7 mg/dL (reference range, 0.6–1.2 mg/dL); hepatic function tests did not reveal any abnormalities. Skin biopsies of the abdomen and axilla demonstrated spongiotic dermatitis with a superficial perivascular infiltrate of lymphocytes, eosinophils, and neutrophils. The eruption gradually resolved over the following weeks after cefepime was discontinued.

Comment

The timing of onset and resolution of both eruptions with respect to cefepime administration as well as prior sensitization with ceftriaxone in the second case supports the diagnosis of cephalosporin-mediated drug eruptions. Morbilliform drug eruptions are the most common manifestation of drug hypersensitivity, accounting for up to 95% of cutaneous reactions.¹ They are characteristically symmetric, widespread, and can progress to erythroderma. A PubMed search, limited to the English language, of articles indexed for MEDLINE using the terms *drug eruption*, *hospitalized patient*, and *islands of sparing* did not reveal any reports of cutaneous drug eruptions manifesting as morbilliform eruptions with islands of sparing. In fact, Magro et al⁷ stated that the morbilliform rash of drug eruptions and viral exanthems presented as “fine pinpoint diffuse erythema lacking islands of skin sparing.”

The diagnosis of a drug eruption is largely based on the typical morphology of the rash, its temporal relationship to the drug ingestion, and exclusion of other clinicopathologic entities. The differential diagnosis of a classic morbilliform eruption is broad and most commonly includes viral exanthems. When considering morbilliform eruptions with islands of sparing, the differential diagnosis is limited and includes pityriasis rubra pilaris, dengue fever, and chikungunya fever.⁸ In addition, a few reports show erythematous indurated plaques with islands of sparing associated with nephrogenic fibrosing dermopathy and calcinosis cutis, though these conditions do not result in a morbilliform eruption.^{9,10}

Skin biopsies of morbilliform drug eruptions often can mimic other diseases and therefore have a limited diagnostic role. The most common histologic finding is a nonspecific superficial perivascular mononuclear cell infiltrate that is indistinguishable from a viral exanthem.¹¹ Less often, interface or lichenoid dermatitis similar to connective-tissue disease–related dermatoses may occur. Spongiotic dermatitis is routinely demonstrated in pustular drug eruptions (ie, acute generalized exanthematous pustulosis) resulting from a variety of medications, commonly β -lactam antibiotics, macrolides, mercury, calcium channel blockers (diltiazem hydrochloride),

furosemide, nonsteroidal anti-inflammatory drugs, and rarely cephalosporins including cefepime.¹² In morbilliform drug eruptions, as seen in these 2 cases, spongiotic dermatitis is a rare histologic manifestation. The largest systematic clinicopathologic evaluation of morbilliform drug eruptions to date included 104 cases; 37 were antibiotic-associated morbilliform drug eruptions, and none were found to have spongiotic dermatitis on histopathologic analysis.¹³ The absence of a preexisting corresponding skin rash in our patients supported the finding of spongiotic dermatitis as a specific histologic manifestation of morbilliform drug eruptions with islands of sparing.

Dermatologists should consider cephalosporin-induced (cefepime-induced) drug hypersensitivity reactions in the differential diagnosis of a morbilliform eruption with islands of sparing. Spongiotic dermatitis with a perivascular mononuclear cell infiltrate on skin biopsy may be suggestive of the diagnosis.

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The authors report no conflict of interest.

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agent. Systemic steroids may help in management. This syndrome may mimic many different pathologic processes. As a result of many nonspecific manifestations, DRESS syndrome may be vastly underreported. Patients on antipsychotic medications also may be treated with anticonvulsants, which may make elucidation of the etiology of the disease even more difficult. Similar phenomena such as anticonvulsant hypersensitivity syndrome and pseudolymphoma may mimic this condition, further obscuring the diagnosis. Although relatively uncommon, a variety of drugs have been implicated in hypersensitivity and it is likely that the incidence of antipsychotic-induced DRESS syndrome is greater than once thought.

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