Acute Generalized Exanthematous Pustulosis
Jaime C. Robertson, MD, and LeAnn Coberly, MD

ABSTRACT
Acute generalized exanthematous pustulosis (AGEP), first described in 1980, is characterized by high fever, a disseminated erythematous rash, and numerous superficial pustules following infection or drug ingestion. Although diagnosed frequently in Europe, this disease is seldom reported in North America. A 75-year-old African-American woman with diabetes, hypertension, and hypothyroidism presented with fever, renal failure, and a disseminated pustular rash on a bed of confluent erythema; she was taking ciprofloxacin and metronidazole. Urinalysis showed numerous white blood cells with a few eosinophils. Urine culture was negative. Skin biopsy showed intraepidermal neutrophilic pustules with underlying neutrophilic infiltrates consistent with AGEP. Rash and renal failure resolved after withdrawal of antibiotics.

AGEP should be considered along with toxic epidermal necrolysis and pustular psoriasis in the differential diagnosis of patients with a pustular rash or drug eruption. We report the first case of AGEP occurring with acute interstitial nephritis.


CASE REPORT AND HISTORY
A 75-year-old African-American woman with diabetes, hypertension, and hypothyroidism presented with a 3-day history of a diffuse, pruritic, erythematous rash with skin peeling (Figure 1). She had undergone an exploratory laparotomy with jejunostomy for small bowel obstruction 2 months prior to presentation. Her course was complicated by an abdominal abscess for which she had received intravenous (IV) cefazolin. The abscess was surgically drained, and she was discharged home to complete a course of ciprofloxacin and metronidazole. Five days into her course she developed an erythematous rash that began on her back and buttocks and spread within a day to cover her entire body. The onset of rash was followed by development of numerous small pustules with areas of confluence (Figures 2 and 3).

PHYSICAL EXAMINATION AND LABORATORY STUDIES
Physical examination revealed an afebrile, obese woman with diffuse erythroderma, discrete areas of superficial desquamation, and small (<1 mm) pustules. Laboratory analysis revealed a white blood cell count of 33 700/µL, a creatinine level of 3.0 mg/dL, and a blood urea nitrogen level of 55 mg/dL. Urinalysis showed numerous white blood cells with a few eosinophils. Urine culture was negative.

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cells, numerous red blood cells, moderate leukocyte esterase, many bacteria, 3 to 5 hyaline casts, and a few eosinophils. Urine culture was negative.

**TREATMENT**

The patient was diagnosed with acute interstitial nephritis and started on IV fluids. The antibiotics were discontinued. She was given topical triamcinolone for her rash. Skin biopsy showed an intraepidermal neutrophilic pustule with underlying neutrophilic infiltrate consistent with acute generalized exanthematous pustulosis (AGEP). Skin cultures remained sterile. During the next 4 days, her rash improved dramatically and her renal failure resolved.

**DISCUSSION**

AGEP was previously confused with pustular psoriasis. In 1980, Beylot et al described AGEP as a separate disease entity on the basis of its acute onset and association with certain drugs.1,2 Patients with AGEP typically present with high fever and an erythematous rash that develops within 2 weeks of starting a medication.2,3 The rash typically begins on the face, axillae, or genitals and spreads within 24 hours to manifest as confluent erythema.2,3 Subsequently, numerous small, sterile, white pustules measuring less than 1 mm appear.2-4 The development of pustulosis is followed by superficial desquamation.

Mucosal involvement occurs in 25% of patients who present with AGEP.2 There is no age or gender predilection.2,3 Histologically, AGEP is characterized by superficial subcorneal and intraepidermal pustules with edema.2,3 Perivascular eosinophilia, leukocytoclastic vasculitis, fibrinoid deposits, and focal necrosis of keratinocytes may also be present.2,3,5,6 Unlike pustular psoriasis, the findings of psoriasiform hyperplasia and papillary acanthosis are typically absent.2,3

Approximately 87% of cases of AGEP are associated with drug exposure,2 but viral infections and contact dermatitis have also been implicated.2,4 Calcium channel blockers, nonsteroidal anti-inflammatory drugs, anticonvulsants, beta-lactam antibiotics, aminoglycosides, and macrolides are the drugs most frequently implicated, though others (including fluoroquinolones and metronidazole) have been reported (Table).2,4,6-7 Sulfonamides are rarely implicated as a cause of AGEP.3

The pathogenesis of AGEP remains uncertain but has been attributed to T-lymphocyte-mediated release of cytokines.5,9 In vitro testing of lymphocytes obtained from patients with AGEP has revealed that release of interferon gamma and

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**Figure 1.** Erythema of the Left Upper Extremity With a Large Area of Superficial Desquamation

**Figure 2.** Pustules With Areas of Confluence and Desquamation on the Left Lateral Thigh

**Figure 3.** Small Pustules With Areas of Confluence and Superficial Desquamation in the Axilla
migration inhibition factor occurs in response to exposure to an offending drug. These tests imply that cell-mediated immunity may be involved in the pathogenesis of AGEP. The cytokine release pattern of cutaneous drug reactions, whether mediated predominantly by T helper-1 or T helper-2 lymphocytes, may depend on the type of drug reaction and the antigen involved.9

Patients with AGEP have an excellent prognosis. Lesions typically resolve within 1 to 2 weeks of withdrawing the offending agent; systemic therapy is not necessary. Hemodynamic support has been required in severe cases and should be considered in patients at risk for cardiac compromise resulting from increased blood flow to the skin. Antipyretics and topical corticosteroids may be of benefit.

This report marks the first known case of AGEP occurring with acute interstitial nephritis. In this case, both ciprofloxacin and metronidazole are implicated. Fluoroquinolones have been reported to cause both AGEP and acute interstitial nephritis, independently. Metronidazole, while implicated in AGEP, has not been reported to cause acute interstitial nephritis. It would be unlikely for 2 discrete drug reactions from 2 different antibiotics to occur simultaneously, though this scenario cannot be ruled out. Polysensitivity to paracetamol and bromhexine has been reported in association with AGEP; both drugs were required to induce in vitro release of interferon gamma. This raises the possibility that the combination of metronidazole and ciprofloxacin may have been necessary to induce the observed reaction. Most likely, reaction to ciprofloxacin is responsible for both conditions. Patch testing may be useful in determining the etiology of cutaneous reactions, though the sensitivity and specificity of such testing in patients with AGEP have yet to be determined. In one report, 7 of 14 patients with AGEP had positive patch test results.17

In patients with a pustular rash or drug eruption, AGEP should be considered as a possible diagnosis, along with toxic epidermal necrolysis (TEN) and pustular psoriasis. AGEP can be distinguished from pustular psoriasis on the basis of the acuity of onset, association with drug administration, and histopathologic features. The cloneliness of pustules may be confused with the positive Nikolsky’s sign of TEN; however, AGEP lesions are more superficial and are readily distinguished by skin biopsy. AGEP is not typically associated with target lesions. The absence of mucosal involvement is an indication of AGEP rather than TEN. However, the presence of mucosal lesions does not establish the diagnosis of TEN since mucosal involvement is present in 25% of patients with AGEP.

Frequently misdiagnosed, AGEP is becoming increasingly recognized as a separate disease entity in the differential diagnosis of cutaneous drug reactions. It is important to distinguish this condition from other cutaneous eruptions to ensure appropriate treatment.

### Table. Drugs Associated With Acute Generalized Exanthematous Pustulosis

<table>
<thead>
<tr>
<th>Drug Class</th>
<th>Category</th>
<th>Name</th>
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<tr>
<td>Antimalarial Agents</td>
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<td>Dexamethasone injection, Hydroxychloroquine</td>
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<td>Antimicrobial Agents</td>
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<td>Gentamicin</td>
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<td>Antifungals</td>
<td>Terbinafine, Itraconazole</td>
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<td>Beta-lactam antibiotics</td>
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<td>Macrolide</td>
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REFERENCES