Case Letter

Daptomycin-Induced Acute Generalized Exanthematous Pustulosis

To the Editor:

Daptomycin is an antibiotic that is increasingly being prescribed for the treatment of gram-positive infections in conditions such as endocarditis, bacteremia, and soft tissue infections. Dermatologic adverse effects associated with daptomycin are not uncommon. Approximately 6.7% of patients taking daptomycin have been reported to develop a rash, and 5.8% have developed pruritus.[1] As the popularity of daptomycin increases for the treatment of drug-resistant *Staphylococcus aureus* and *Enterococcus* infections, it is important for physicians to be aware of the potential dermatologic complications that may be associated with the use of this novel antibiotic in clinical practice.

A 56-year-old woman was admitted to our hospital with a fever (temperature, 38.7°C), hypotension (blood pressure, 94/54), and a new truncal rash. The patient had undergone knee replacement surgery 5 weeks prior. She developed an infection 2 weeks following surgery and was started on vancomycin, levofloxacin, and rifampin. She continued on this regimen for 3 weeks. Four days prior to presentation the patient developed erythema and edema of the face consistent with red man syndrome; levofloxacin was discontinued and vancomycin and rifampin were replaced with daptomycin (500 mg/10 mL). When the patient was admitted to our hospital 4 days later, vasopressor support was initiated for presumed septic shock due to infection from a peripherally inserted central catheter line. The white blood cell count as well as absolute neutrophil and eosinophil levels were within reference range, but liver function tests were elevated (aspartate aminotransferase, 353 U/L [reference range, <40 U/L]; alanine aminotransferase, 386 U/L [reference range, <40 U/L]). Physical examination revealed confluent erythematous macules with scattered pinpoint pustules on the neck, trunk, arms, and legs (Figure 1). There was facial edema but no lymphadenopathy was noted.

Histologic examination revealed intraepidermal neutrophils with focal aggregation into subcorneal pustules. Papillary dermal edema was prominent with a superficial perivascular and interstitial inflammatory

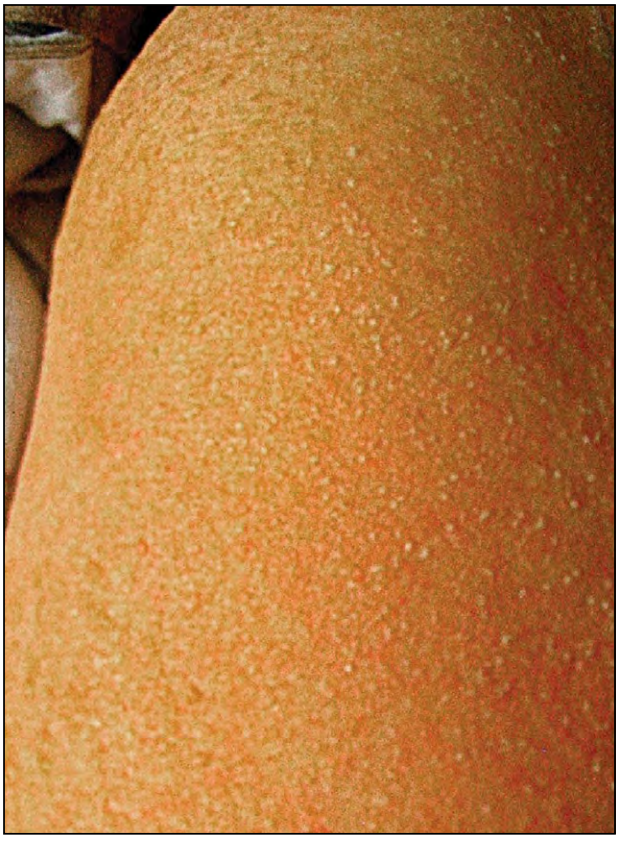

Figure 1. Erythematous macules and patches with scattered pinpoint pustules on the right upper arm and shoulder.

Dr. Gordon Spratt is from The Ronald O. Perelman Department of Dermatology, New York University School of Medicine, New York. Drs. Schmidt and Kantrow are from the Vanderbilt University School of Medicine, Nashville, Tennessee.

The authors report no conflict of interest.

Correspondence: Elizabeth A. Gordon Spratt, MD, The Ronald O. Perelman Department of Dermatology, New York University School of Medicine, 240 E 38th St, Floor 11, New York, NY 10016 (elizabeth.gordon@nyumc.org).

infiltrate of lymphocytes, neutrophils, and numerous eosinophils (Figure 2). These findings were consistent with acute generalized exanthematous pustulosis (AGEP). All blood cultures were negative. Within a few days the edema and erythema subsided, leaving desquamating erythematous patches. The patient's other medications included simvastatin, citalopram, levothyroxine, hydrocortisone cream, celecoxib, and pramipexole, all of which she had been taking for at least 3 years. She also was taking oxycodone hydrochloride and warfarin, which were initiated after the knee replacement. Based on the patient's history as well as the clinical and histologic appearance, she was diagnosed with daptomycin-induced AGEP.

Acute generalized exanthematous pustulosis is a less common acute febrile drug eruption consisting of small, primarily nonfollicular sterile pustules arising within large areas of edematous erythema, often beginning on the face or intertriginous zones and then disseminating. There may be associated burning or pruritus. Edema of the face and hands is not uncommon and mucous membranes may be involved. The time from drug administration to skin eruption is relatively short, usually less than 2 days. The lesions generally last 1 to 2 weeks after onset and spontaneously resolve with superficial desquamation.

Although AGEP most commonly is triggered by β-lactam and macrolide antibiotics, AGEP also has been associated with chromium supplements,[2] seasonings containing urushiol, and parasitic or viral infections.[3] A multinational case-control study by Sidoroff et al[4] showed no increased family or personal history of psoriasis in patients with AGEP; our patient also did not have a history of psoriasis.

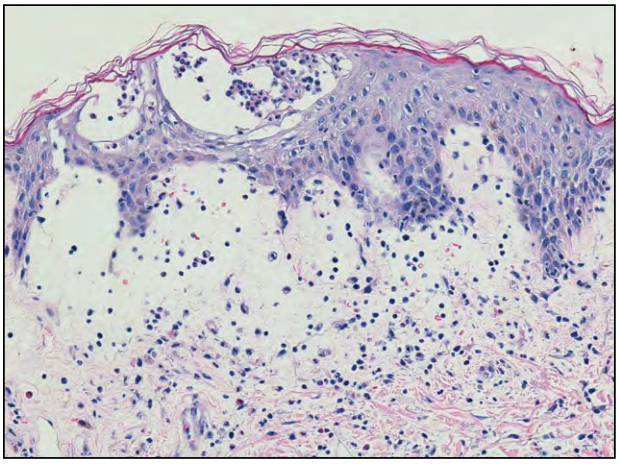

Figure 2. Spongiform pustules within the superficial epidermal layers, prominent edema of the papillary dermis, and a mixed perivascular infiltrate of predominantly neutrophils as well as eosinophils (H&E, original magnification ×20).

Daptomycin is a semisynthetic lipopeptide antibiotic derived from the fermentation of *Streptomyces roseosporus* that exerts its bactericidal action by disrupting plasma membrane function and inducing cell depolarization. Daptomycin is active against many gram-positive bacteria including vancomycin-resistant *Enterococcus faecalis* and methicillin-resistant *S aureus*.[5,6] It currently is approved for the treatment of complicated skin and skin structure infections due to gram-positive cocci and bacterial endocarditis.

In animal studies, the most common adverse effects of treatment with daptomycin were myopathy and elevated serum creatine kinase levels, which were reversible on discontinuation of the drug.[5] Thus weekly measurements of creatine kinase levels are recommended while receiving daptomycin therapy, especially if the patient also is taking a 3-hydroxy-3-methylglutaryl coenzyme A reductase inhibitor. Other common adverse effects in human trials include eosinophilic pneumonia and diarrhea associated with *Clostridium difficile* infection.[1]

In phase 3 human trials, dermatologic adverse effects associated with daptomycin were not uncommon, affecting up to 30% of patients in some trials. Side effects included rash (4.3%–6.7%), generalized erythema (5%), pruritus (2.8%–5.8%), heat rash (<1%), and eczema (<1%).[1] In postmarketing data collection worldwide, a vesiculobullous rash with or without mucous membrane involvement was reported in an unknown percentage of patients.

Our case of a pustular eruption associated with the use of daptomycin is unique. In our patient, the clinical and histologic presentation was consistent with the diagnosis of AGEP. Based on the patient's history of starting daptomycin 4 days prior to the onset of symptoms, we believe that the drug was associated with the development of AGEP. She had not recently undergone any other medication changes, as she had been taking her other medications for at least 3 years with the exception of warfarin and oxycodone hydrochloride, which were initiated 5 weeks prior to the eruption.

Because of its unique mechanism of action as well as the prevalent phenomenon of antibiotic resistance, daptomycin is increasingly used for the treatment of complicated skin and skin structure infections caused by gram-positive organisms. As the use of daptomycin increases, it is important for physicians to be aware of its potential cutaneous complications.

Elizabeth A. Gordon Spratt, MD
Adriana N. Schmidt, MD
Sara M. Kantrow, MD

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