Midodrine-Induced Acute Generalized Exanthematous Pustulosis

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Practice Points

- Although antibiotics are most commonly associated with acute generalized exanthematous pustulosis (AGEP), nonantibiotic agents also can cause AGEP.
- Acute generalized exanthematous pustulosis associated with nonantibiotic agents often manifests after a longer time interval from initial drug administration compared to AGEP associated with antibiotic agents.

Acute generalized exanthematous pustulosis (AGEP) is an acute sterile pustular eruption most commonly induced by medications. We present a case of AGEP with erythroderma following use of midodrine in a 58-year-old man. Although antibiotics are most commonly implicated in AGEP, we emphasize that nonantibiotic agents also may cause AGEP, which often manifests after a longer time interval compared to antibiotic-associated AGEP.

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Acute generalized exanthematous pustulosis (AGEP) is an acute eruption of numerous nonfollicular sterile pustules in an erythematous background, often beginning on the face and intertriginous areas and subsequently progressing to a generalized distribution with fever and leukocytosis.[1] Acute generalized exanthematous pustulosis is most commonly caused by medications[1,2] and rarely has been associated with viral (eg, enterovirus) infections[1] and exposure to inorganic compounds (eg, mercury)[1] or contrast agents.[3] We report a unique case of a 58-year-old man who developed AGEP from the use of midodrine.

Case Report

A 58-year-old man with no known drug allergies presented to the hospital with a pruritic generalized cutaneous eruption that began abruptly 1 day prior to admission. The patient's medical history was remarkable for alcoholic cirrhosis, refractory ascites, supraventricular tachycardia, gout, hypertension, and osteoarthritis. He denied personal or family history of skin disease, including psoriasis. Twenty-two days prior to admission he was started on midodrine (20 mg 3 times daily), and 4 days prior to admission he was started on rifaximin (550 mg twice daily) for treatment of decompensated cirrhosis. His other outpatient medications included lactulose (10 g twice daily) and guaifenesin (100 mg daily as needed). A review of systems was notable for pruritus but was otherwise unremarkable.

On admission, a skin examination revealed numerous 2- to 9-mm, coalescing, red macules and edematous papules on the trunk, bilateral upper and lower extremities, and face. No facial edema, involvement of mucous membranes, or lymphadenopathy was observed. A laboratory workup revealed an elevated white blood cell count (12,200/μL [reference range, 4500–11,000/μL]) with 87% (reference range, 56%) neutrophils and no eosinophils (reference range, 2.7%). Given these findings, the patient was diagnosed with a morbilliform drug eruption suspected to be secondary to rifaximin, largely because the drug

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was started 4 days prior to rash onset; thus rifaximin was discontinued. Triamcinolone ointment 0.1% was applied twice daily to all skin starting on day 1 of the patient's hospital admission and was continued without tapering for 4 full weeks until the patient was discharged. Systemic steroids were not used.

The patient subsequently became febrile (temperature, 38.2°C) and on his fourth day of admission was found to have numerous 2- to 4-mm superficial pustules on the bilateral lower extremities. On his fifth day of admission he became erythrodermic with intertriginous and lower extremity collarettes of scale at sites of unroofed pustules (Figures 1 and 2).

A skin biopsy from the proximal aspect of the left upper arm performed on the day of admission (Figure 3) as well as a repeat biopsy of an erythrodermic area (without clinically visible pustules) on the distal aspect of the right thigh on day 6 of admission (Figure 4) each revealed numerous subcorneal pustules, spongiosis, and a perivascular and interstitial mixed inflammatory infiltrate with neutrophils and eosinophils. Gram and periodic acid–Schiff stains were negative for bacterial and fungal organisms. These histopathologic findings, in concert with his evolving skin lesions, favored a revised diagnosis of AGEP.

The decision was made to discontinue midodrine in addition to the previously discontinued rifaximin with a plan to reintroduce each drug at 2 different time points to identify the culprit agent. Accordingly, on day 4 midodrine was stopped for 5 days and the patient's erythema substantially improved with

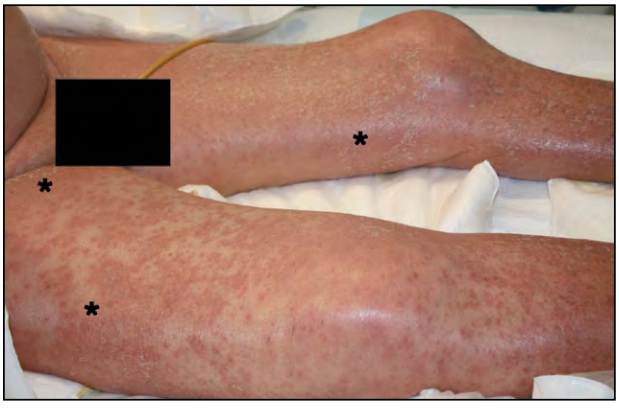

Figure 1. Acute generalized exanthematous pustulosis involving the bilateral lower extremities with numerous collarettes of scale (asterisks) visible in the bilateral inguinal folds as well as on the thighs and shins.

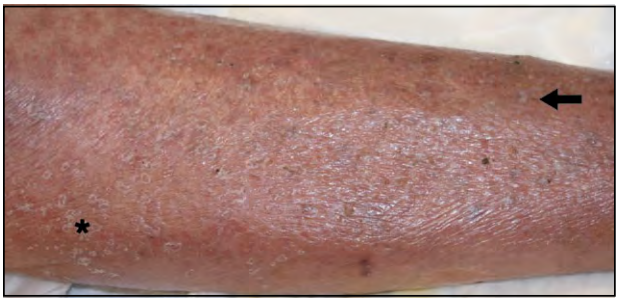

Figure 2. Erythroderma involving the left lower extremity with admixed superficial pustules (arrow) and collarettes of scale (asterisk), which were indicative of unroofed pustules.

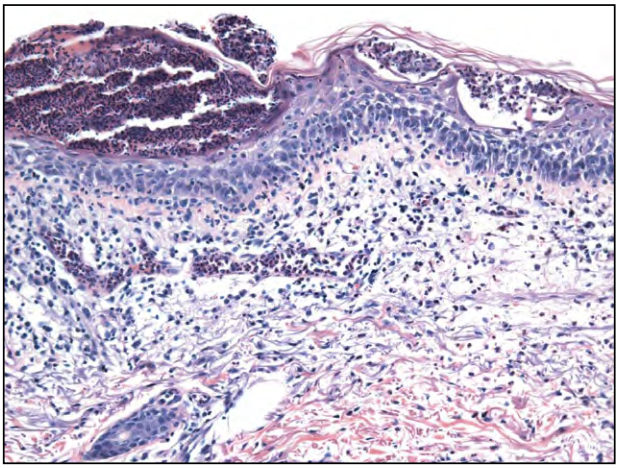

Figure 3. Microscopic examination of a punch biopsy obtained on the day of hospital admission showed subcorneal pustules with aggregates of neutrophils, spongiosis, and perivascular and interstitial infiltrate with neutrophils and eosinophils (H&E, original magnification ×20).

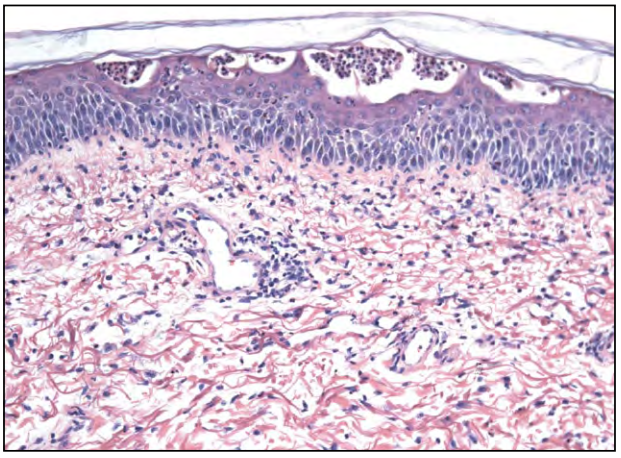

Figure 4. Microscopic examination of a punch biopsy obtained from erythrodermic skin on day 6 of hospital admission demonstrated histologic features of acute generalized exanthematous pustulosis similar to the original biopsy from day 1 of admission, including subcorneal pustules (H&E, original magnification ×20).

resolution of pustules. Midodrine was then restarted on day 9 of admission, and within 48 hours he developed new peripheral eosinophilia (absolute eosinophil count, 1274/μL [reference range, 0–450/μL]) (Figure 5). Rifaximin was reintroduced 2 days later after the patient's clinical and hematologic manifestations of AGEP progressed, which decreased the likelihood that rifaximin was responsible for the AGEP. Both midodrine and rifaximin were discontinued on day 14.

Unfortunately, out of medical necessity, the patient was restarted on midodrine on day 18 of admission (his third course), and he quickly developed worsening erythema and numerous new pustules on the right side of the back and the right shin. Midodrine was permanently discontinued at day 21, and the patient's cutaneous eruption as well his peripheral eosinophilia completely resolved without recurrence by day 32.

Comment

Recognition of AGEP as a distinct entity from pustular psoriasis began with Baker and Ryan[4] in 1968; they isolated 5 cases in which the pustular eruption occurred over a short duration in patients without a history of psoriasis. Clinically, AGEP is characterized by the acute evolution of several dozen small, mostly nonfollicular pustules arising in the setting of widespread edematous erythema. It often is associated with neutrophilic leukocytosis and fever (temperature, >38°C), with spontaneous resolution of pustules.[1,5] Histopathologic changes consist of spongiform subcorneal and/or intraepidermal pustules, edema of the papillary dermis and perivascular infiltrates with neutrophils, and exocytosis of some eosinophils.[5]

Midodrine is a selective α_1-adrenergic receptor agonist used in the treatment of orthostatic hypotension as well as for off-label treatment of stress urinary incontinence and hepatorenal syndrome.[6-11] Cutaneous eruptions associated with midodrine are infrequent. The chemical structure of midodrine has 1 aromatic ring; the presence of aromatic rings in anticonvulsant medications has been linked to the development of anticonvulsant hypersensitivity syndrome and DRESS (drug reaction with eosinophilia and systemic symptoms) syndrome.[12-14] Thus it is plausible to hypothesize that the aromatic ring in midodrine is the chemical moiety responsible for the AGEP reaction.

Our patient developed signs of AGEP 22 days following the initiation of midodrine, which is consistent with the time interval previously reported for AGEP caused by nonantibacterial drugs.[1] Roujeau et al[1] found that the mean time interval to disease onset is notably longer for nonantibacterial drugs (mean [standard deviation], 18 [11] days) compared to antibacterial agents (mean [standard deviation], 2.5 [3.2] days). The time frame over which our patient developed AGEP is consistent with midodrine as the culprit medication.

Conclusion

Numerous drugs may cause AGEP, prompting recognition and discontinuation of the causative agent for disease management. Although antibacterial medications are the main drug class implicated in

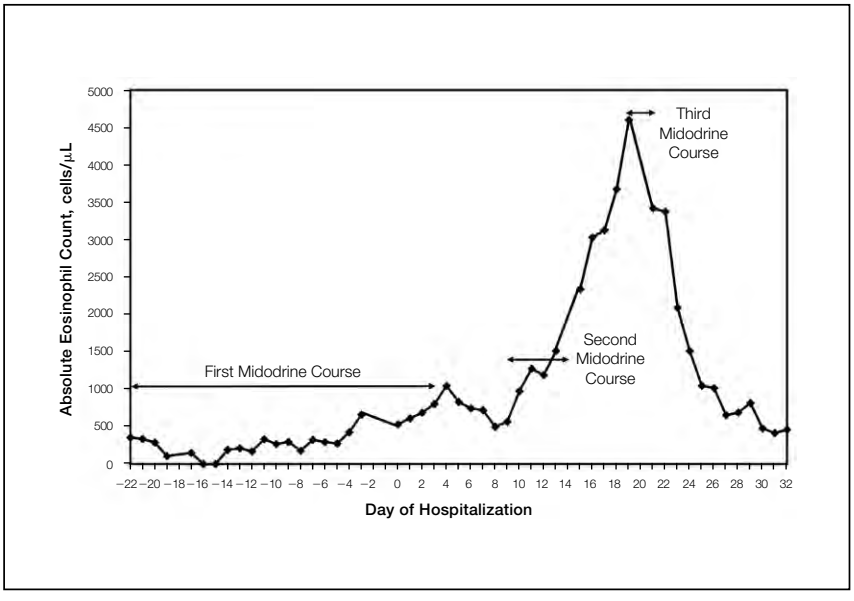

Figure 5. Absolute eosinophil counts (reference range, 0–450/μL) prior to and during the patient's hospitalization. Negative values for "day of hospitalization" indicate the days prior to the patient's admission, with hospital day 0 corresponding to the day of admission. Horizontal arrows denote the 3 courses of midodrine the patient received.

AGEP,[1] we emphasize the importance of considering nonantibacterial medications as a potential cause of AGEP. It also should be noted that the latter may cause the eruption after a longer time interval than antibiotics. We report midodrine as an additional medication causing AGEP.

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