Acute generalized exanthematous pustulosis sine pustules: A case series

Steven A. Svoboda, MD, Elizabeth L. Bisbee, MD, Nicole Bender, MD, and Kiran Motaparthi, MD
Gainesville, Florida

Key words: Acute generalized exanthematous pustulosis; acute generalized exanthematous pustulosis without pustules; drug eruption; inpatient dermatology; severe cutaneous adverse reaction; subcorneal pustular dermatitis.

INTRODUCTION

Acute generalized exanthematous pustulosis (AGEP) is a severe cutaneous adverse reaction that classically presents with numerous pinpoint, sterile pustules overlying erythematous and edematous plaques. The onset of AGEP typically occurs within 2 to 5 days after exposure to the offending agent—most commonly β-lactam antibiotics. Skin findings may also be accompanied by signs of systemic involvement, including fever, neutrophilia, mildly elevated hepatic enzymes, creatinine, and C-reactive protein. The histopathology of AGEP demonstrates subcorneal and/or intraepidermal pustules with papillary dermal edema and a dermal infiltrate containing neutrophils and eosinophils.[1-3]

The pathophysiology of AGEP is poorly understood; however, the recruitment and activation of neutrophils appears to be driven by aberrant signaling from cytokines such as interleukin 17, interleukin 36, granulocyte-macrophage colony-stimulating factor, tumor necrosis factor α and chemokine (C-X-C motif) ligand 8/interleukin 8.[1,2] Patients with AGEP have a favorable prognosis with resolution of signs and symptoms within days following discontinuation of the causative agent. Although rare, complications such as superimposed infections, can be fatal. Thus, treatment primarily consists of surveillance for infections and supportive care.[1,2,4] Herein, we report of 8 patients with histopathology-confirmed AGEP who presented without pustules on clinical examination.

Abbreviations used:

AGEP: acute generalized exanthematous pustulosis
DRESS: drug rash with eosinophilia and systemic symptoms

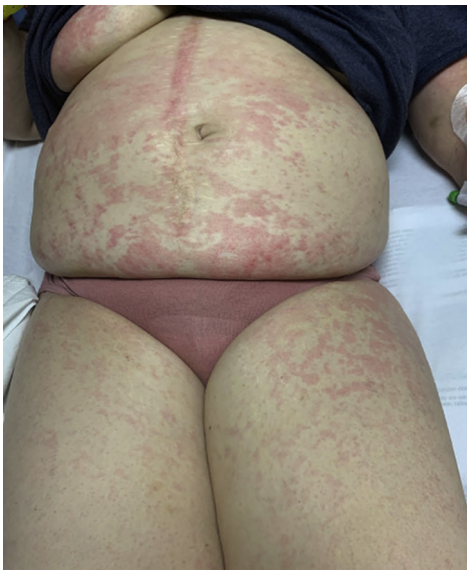

Fig 1. Acute generalized exanthematous pustulosis. Morbilliform erythema of the chest, abdomen, and thighs, without clinically evident pustules at presentation.

CASE SERIES

Atypical presentations of AGEP resembling toxic epidermal necrolysis or drug-induced hypersensitivity syndrome have been described; however, there are no documented cases of AGEP occurring without clinically evident pustules (Fig 1).[2,4] Neutrophilia and transaminitis were observed in 7 out of 8 patients and 4

From the Department of Dermatology, University of Florida College of Medicine, Gainesville.
Funding sources: None.
IRB approval status: Not applicable.
Correspondence to: Kiran Motaparthi, MD, Department of Dermatology, University of Florida College of Medicine, 4037 NW 86th Terrace, 4th Floor, Gainesville, FL 32606. E-mail: kmotaparthi@dermatology.med.ufl.edu.

JAAD Case Reports 2022;23:24-6.
2352-5126

https://doi.org/10.1016/j.jdcr.2022.02.009

Table I. Summary of clinical and histologic findings of 8 patients diagnosed with acute generalized exanthematous pustulosis (AGEP) and corresponding EuroSCAR scores

Patient	Age/ sex	Race	Clinical differential diagnosis	Histopathology	Suspected offending medication(s)	Systemic features	Complete resolution without sequelae	EuroSCAR validation score
1	67/F	Caucasian	Scarlet fever, viral exanthem, morbilliform drug eruption	Neutrophilic parakeratosis, dermal edema and superficial neutrophilic infiltrate	Ceftriaxone, cefepime	Neutrophilia	Yes	6
2	58/F	Caucasian	Morbilliform drug eruption, intertrigo with edema bullae	Neutrophilic spongiosis	Ciprofloxacin	Neutrophilia, mild AKI	Lost to followup	6
3	31/F	Hispanic	Morbilliform drug eruption, early DRESS, miliaria	Subcorneal neutrophils, neutrophilic parakeratosis, and dermal eosinophils	TMP/SMX	Neutrophilia, transaminitis	Yes	6
4	89/M	African-American	Morbilliform drug eruption, disseminated zoster	Spongiotic dermatitis with eosinophils and intraepidermal neutrophilic pustules	Torsemide	Transaminitis	Yes	5
5	28/F	Hispanic	AGEP	Neutrophilic spongiosis	Vancomycin	Neutrophilia, transaminitis	Yes	6
6	38/F	Caucasian	Evolving drug eruption, herpesvirus infection, contact dermatitis	Subcorneal pustular dermatitis, papillary dermal edema and dermal eosinophils	TMP/SMX, ciprofloxacin, azithromycin	Neutrophilia, eosinophilia, transaminitis	Yes	6
7	61/M	Caucasian	AGEP, DRESS	Neutrophillic parakeratosis, papillary dermal edema, superficial and deep perivascular infiltrate of neutrophils and eosinophils	TMP/SMX, azithromycin	Neutrophilia, eosinophilia, AKI, transaminitis	Yes	6
8	71/F	Caucasian	Morbilliform drug eruption, AGEP	Subcorneal pustular dermatitis	Cefazolin, cefepime	Neutrophilia	Yes	6

AGEP, Acute generalized exanthematous pustulosis; *AKI,* acute kidney injury; *DRESS,* drug reaction with eosinophilia and systemic symptoms; *EuroSCAR,* European Severe Cutaneous Adverse Drug Reactions; *F,* female; *M,* male; *TMP/SMX,* trimethoprim/sulfamethoxazole.

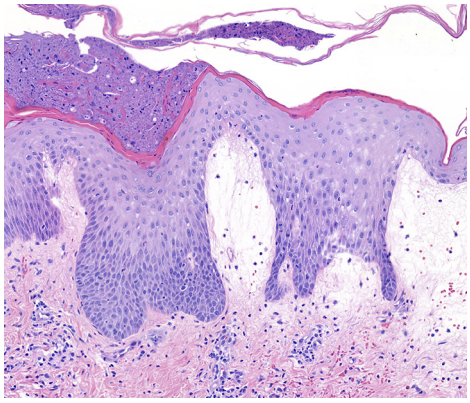

Fig 2. Acute generalized exanthematous pustulosis (AGEP). From the patient pictured in Fig 1, a punch biopsy demonstrated typical features of AGEP: Orthokeratosis overlying a subcorneal pustular dermatitis with irregular epidermal hyperplasia, marked papillary dermal edema, and a dermal infiltrate containing lymphocytes, neutrophils, and eosinophils (Hematoxylin-eosin stain; original magnification: ×200).

out of 8 patients, respectively (Table I). The offending agents included trimethoprim-sulfamethoxazole, torsemide, azithromycin, ciprofloxacin, and cephalosporin antibiotics (Table I). Biopsies were performed in all patients and demonstrated histopathologic findings consistent with AGEP (Fig 2). All patients had an AGEP validation score greater than 5, indicating probable AGEP, based on the EuroSCAR (European Severe Cutaneous Adverse Drug Reactions) diagnostic criteria (Table I).[5]

DISCUSSION

AGEP "sine" (without) pustules has not been previously described. Rather than a distinct disorder, these findings support a subtle clinical variant or an early manifestation of AGEP. Prompt resolution without significant sequelae following drug cessation was observed in all 8 of these patients, and distinction from morbilliform drug eruption is challenging without histopathology. Therefore, it is possible that this variant of AGEP is underdiagnosed. Given that AGEP has the potential to produce life-threatening complications, awareness of this presentation is important in order to prevent misdiagnosis as morbilliform drug eruption, drug rash with eosinophilia and systemic symptoms (DRESS) syndrome, or viral exanthem.

The onset of AGEP is typically more rapid than that observed in morbilliform drug eruption or DRESS. Morbilliform drug eruptions and DRESS usually appear 1 to 2 weeks and 2 to 8 weeks after initiation of the culprit drug, respectively.[4,5] Nevertheless, histopathologic evaluation may be helpful for patients with morbilliform-like exanthems and unclear medication history in order to exclude AGEP without pustules.[4,5]

Conflicts of interest

None disclosed.

REFERENCES

1. Feldmeyer L, Heidemeyer K, Yawalkar N. Acute generalized exanthematous pustulosis: pathogenesis, genetic background, clinical variants and therapy. *Int J Mol Sci*. 2016;17(8):1214. https://doi.org/10.3390/ijms17081214
2. Szatkowski J, Schwartz RA. Acute generalized exanthematous pustulosis (AGEP): a review and update. *J Am Acad Dermatol*. 2015;73(5):843-848. https://doi.org/10.1016/j.jaad.2015.07.017
3. Hoetzenecker W, Nägeli M, Mehra ET, et al. Adverse cutaneous drug eruptions: current understanding. *Semin Immunopathol*. 2016;38(1):75-86. https://doi.org/10.1007/s00281-015-0540-2
4. Kostopoulos TC, Krishna SM, Brinster NK, Ortega-Loayza AG. Acute generalized exanthematous pustulosis: atypical presentations and outcomes. *J Eur Acad Dermatol Venereol*. 2015;29(2):209-214. https://doi.org/10.1111/jdv.12721
5. De A, Das S, Sarda A, Pal D, Biswas P. Acute generalised exanthematous pustulosis: an update. *Indian J Dermatol*. 2018;63(1):22-29. https://doi.org/10.4103/ijd.IJD_581_17