## Title
Cetirizine-induced Acute Generalized Exanthematous Pustulosis: a serious reaction to a commonly used drug



## Journal
Dermatology Online Journal, 20(5)

## Authors
Badawi, Ahmed H
Tefft, Kimberly
Fraga, Garth R
et al.

## Publication Date
2014

## DOI
10.5070/D3205022613

**Volume 20 Number 5**
**May 2014**

**Case Presentation**

# Cetirizine-induced Acute Generalized Exanthematous Pustulosis: a serious reaction to a commonly used drug

**Ahmed H. Badawi PhD,[1] Kimberly Tefft MD[2], Garth R. Fraga MD[3], Deede Y. Liu MD[2]**

**Dermatology Online Journal 20 (5): 7**

**[1]School of Medicine; [2]Division of Dermatology; and [3]Department of Pathology and Laboratory Medicine; University of Kansas Medical Center, Kansas City, KS**

**Correspondence:**

Deede Liu, M.D.
Division of Dermatology
University of Kansas Medical Center
3901 Rainbow Boulevard
Kansas City, KS 66160
Phone: (913) 588-2032
Fax: (913) 588-8761
E-mail: dliu@kumc.edu

## Abstract

Acute generalized exanthematous pustulosis (AGEP) is an abrupt cutaneous adverse reaction usually in response to medications. It is generally a self-limiting disease if diagnosed promptly and the offending agent discontinued. Cetirizine, a commonly used anti-histamine medication for the treatment of allergic diseases has few reported side effects and is normally well-tolerated and effective. Herein, the first reported case of cetirizine induced AGEP is presented, followed by a discussion of the clinical and pathological aspects of this adverse cutaneous reaction to a widely used drug. Awareness of this reaction is vital owing to the extensive use of cetirizine and the importance of drug cessation once the reaction is identified. Lastly, other pustular cutaneous reactions may present similarly and therefore accurate identification of this disease can prevent unnecessary diagnostic testing.

## Introduction

Acute generalized exanthematous pustulosis (AGEP) is an adverse cutaneous reaction to various medications. It manifests with the abrupt onset of small non-follicular sterile pustules arising within an edematous erythematous base. Systemic symptoms are mild and the disease normally resolves spontaneously after the inciting agent is withdrawn. There is no apparent male or female predominance and the reaction can occur at any age. There are no reliable data on the incidence in the United States. The European severe cutaneous adverse reactions (EuroSCAR) study found an incidence of 1-5 per million per year [1].

Cetirizine is a selective second generation histamine-1 receptor antagonist (more accurately, an inverse agonist) that is widely used for the treatment and management of allergic rhinitis, urticaria, atopic dermatitis, and other allergic diseases [2]. Cetirizine has a broad safety profile and is well tolerated. Somnolence (14%), fatigue (6%), and dry mouth (5%) are the most common adverse effects associated with cetirizine in the adult population (≥12 years), whereas headache (11-14%), pharyngitis (3-6%), abdominal pain (4-6%), coughing (3-4%), somnolence (2-4%), and epistaxis (2-4%) have been reported in the pediatric population (6 months – 11 years) [2]. Cutaneous adverse reactions are rare but there are reports of urticarial eruptions [3], fixed drug eruptions [4], and generalized morbilliform eruptions with pruritus [5] linked to cetirizine. We report the first case of AGEP induced by cetirizine.

## Case synopsis

An eleven-year-old girl with history of seasonal allergic rhinitis and type 1 diabetes mellitus presented with a worsening pruritic eruption of four days duration associated with emesis and malaise. She denied any recent viral illnesses. The eruption started on the face and spread to the chest, arms, and bilateral axilla, sparing the abdomen (Figure 1). Mucosal surfaces were spared. The erythematous macules developed pustules within 48 hours. The patient denied fever and joint pain. Hydrocortisone cream, calamine lotion, triple antibiotic ointment, and oral diphenhydramine (given by the patient's primary care provider) failed to provide any relief. Two days prior to the eruption, the patient began taking 5 mg of cetirizine daily. No other medications or supplements were started within two months prior to the development of the eruption. Laboratory testing revealed neutrophilia of 9770/µL (normal, 1800-7000/µL), normal eosinophil count of 30/µL (normal, <650/µL), elevated erythrocyte sedimentation rate of 18 mm/h (normal, 0-10 mm/h), and an elevated C-reactive protein of 6.31 mg/dL (normal, <1.0 mg/dL). Bacterial culture of the pustule was negative. A cutaneous shave biopsy was performed and demonstrated non-follicular subcorneal pustules comprised of neutrophils with rare eosinophils and mild papillary edema (Figure 2) consistent with AGEP. Cetirizine was discontinued and the patient was started on loratidine. In addition, during the hospital stay, triamcinolone 0.1% ointment was applied on the affected areas twice a day for three days. Systemic steroids were avoided given her history of diabetes. On follow up, the patient reported complete resolution of erythema and pustules after 14 days.

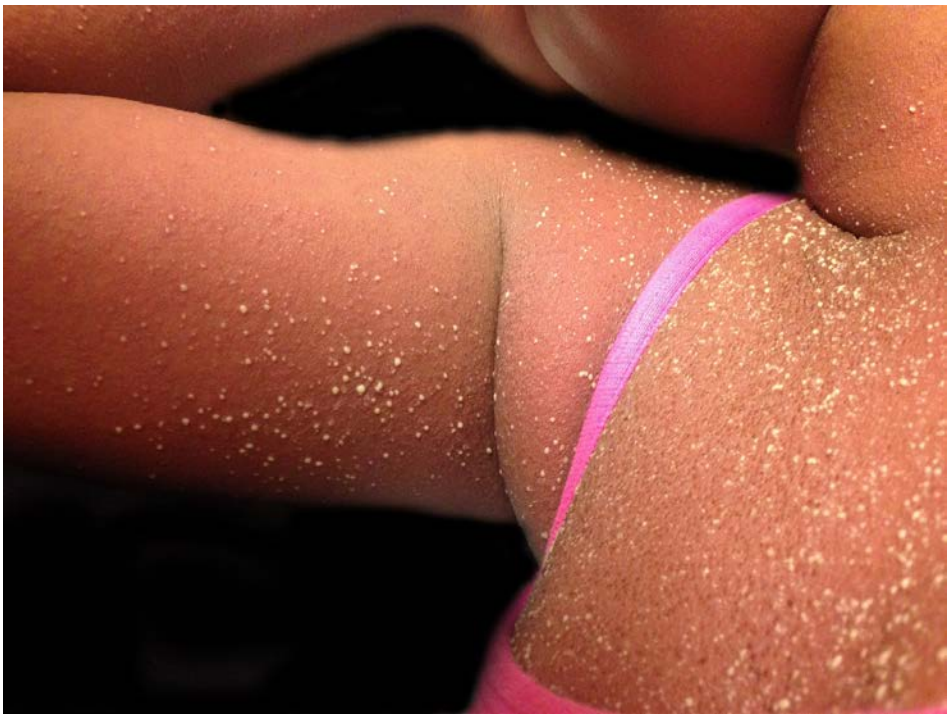

**Figure 1.** Acute generalized exanthematous pustolosis affecting the arm, axilla, and chest of an eleven-year-old girl two days after cetirizine administration.

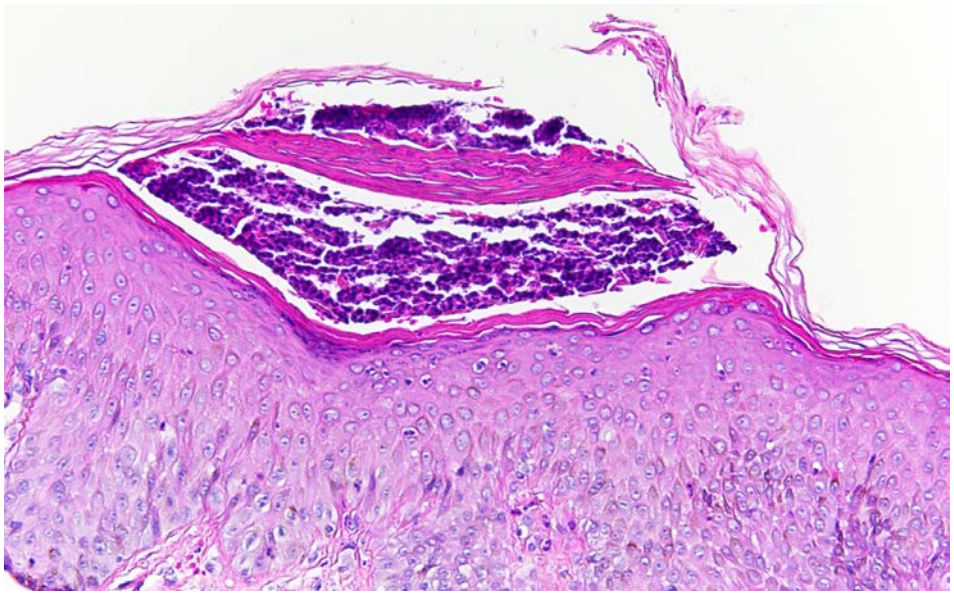

**Figure 2.** Biopsy demonstrates non-follicular subcorneal pustules comprised of neutrophils with rare eosinophils, and mild papillary edema.

## Discussion

AGEP is characterized by an abrupt onset of widespread edematous erythema, which becomes quickly covered by numerous small (<5 mm) non-follicular subcorneal sterile pustules [1]. The first signs of disease can appear as rapidly as a few hours to three weeks after exposure to the causative agent, but the mean is 5.1±7.9 days according to a review of 63 AGEP cases [6]. These findings are typically associated with fever and leukocytosis owing to neutrophilia. Other minor findings include mild mucous membrane involvement (20%), eosinophila (33.3%), lymphadenopathy, reduced creatinine clearance, and mildly elevated aminotransferases [1]. Histopathology demonstrates subcorneal and/or intraepidermal pustules, papillary dermis edema, neutrophilic and/or occasional eosinophilic perivascular infiltration, and possible vasculitis and keratinocyte necrosis [1]. Pustules disappear within 5-10 days and spontaneous healing occurs 10-15 days after termination of the offending agent, followed by desquamation of the stratum corneum. The disease is self-limited, although there is a 1-2% mortality rate as a result of a high fever or secondary infection, primarily in elderly patients with other comorbidities [1, 7].

Sidoroff et al. proposed a scoring system based on 5 criteria to make the diagnosis of AGEP [1]. This scoring algorithm would label the diagnosis as excluded, possible, probable, or definite according to the morphological and histological findings and clinical course of the presenting patient. The differential diagnosis of pustular lesions that are not readily distinguishable from AGEP include toxic epidermal necrolysis, drug rash with eosinophilia and systemic symptoms (DRESS), subcorneal pustular dermatosis (Sneddon-Wilkinson disease), pustular vasculitis, and pustular psoriasis (von Zumbusch type) [7]. Non-follicular subcorneal pustules, abrupt onset, and rapid resolution are the defining features of AGEP and are important for differentiating it from other cutaneous diseases with pustular eruptions.

The causes of AGEP vary widely and cases reporting new causative agents continue to appear. Drug-induced AGEP makes up the majority of the cases (approximated to be greater than 90%), with antibiotics being the most common [1]. Some of the most notorious AGEP-inducing drugs include the beta-lactam antibiotics (penicillins, cephalosporins, and aminopenicillins), macrolides, calcium-channel blockers (diltiazem in particular), antimalarials (hydroxychloroquine and chloroquine), quinolones, sulfonamides, terbinafine, carbamazepine, and acetaminophen [1, 8]. There are many reports of viral and bacterial infections inducing AGEP [6], but a multinational case-control study demonstrated that there was no significant evidence for the link of infections to AGEP. Instead they concluded that these reported cases were induced by medications prescribed for the infections [8].

**Table 1**

| Drug | Gender/Age/ Race | Evolution (days) | Fever | Neutrophilia | Eosinophilia | Distribution Pattern | Treatment | Histology | Resolution (days) | Reference |
|---|---|---|---|---|---|---|---|---|---|---|
| Cetirizine | Female/11/ African American | 6 | - | + | - | Face, chest, arms, and bilateral axilla<br><br>No abdomen and mucosal involvement | Triamcinolone 0.1% ointment twice/day for 3 days | Non-follicular subcorneal pustules comprised of neutrophils and eosinophils with mild papillary edema | 14 | Current |
| Clemastine | Male/41/NR | 8 | + | + | NR | Face, neck, trunk, extremities, palms, and volar and interdigital aspects of fingers<br><br>No mucosal involvement | Prednisone 40mg/day for 4 days | Intraepidermal pustules comprised of neutrophils and eosinophils with edema, mixed cell inflammation and extravasated erythrocytes in subjacent dermis | 7 | [9] |
| Diphenhydramine | Female/67/ Japanese* | 2 | + | + | -* | Trunk and extremities<br><br>No mucosal involvement | Betamethasone ointment | Subcorneal neutrophilic pustules and mixed cell inflammation in subjacent dermis | 3 | [10] |
| Hydroxyzine | Male/67/NR | 1 | + | + | NR | Neck, extremities, trunk, and axilla<br><br>No scalp, palms, soles, and mucosal involvement | None | Subcorneal pustule with neutrophils, apoptotic keratinocytes and mixed cell inflammation and edema in subjacent dermis | 3 | [11] |

Table 1. H1-receptor antagonist-associated acute generalized exanthematous pustolosis.
*Per contact with corresponding author of case report. NR; not reported.

Other H1-receptor antagonists such as clemastine [9], diphenhydramine [10], and hydroxyzine [11] have been shown to induce an AGEP reaction (Table 1). Interestingly, amongst the list, cetirizine is the only second generation H1-receptor antagonist that has induced AGEP. Consistent with previously published reports on drug-induced AGEP, H1-receptor antagonists demonstrate similar demographical, clinical, and histological findings.

The pathogenesis of AGEP is unknown, but positive epicutaneous patch testing, immunohistochemistry of cutaneous biopsies, and *in vitro* studies suggest an allergic reaction during which drug specific $CD4^+$ and $CD8^+$ T cells play a crucial role [12]. Genotyping of patients with AGEP reveals that human leukocyte antigen genes B51, DR11, and DQ3 are more frequent than in the average population [13], suggesting a possible genetic predisposition. Although most hypersensitivity reactions exhibit eosinophilia, neutrophilic inflammation is the hallmark of AGEP. T-cells are activated peripherally and then migrate to the skin where they mediate keratinocyte destruction, leading to vesicle formation. At the lesion site, both T-cells and keratinocytes produce large amounts of the neutrophil-attracting cytokine, interleukin (IL)-8, which results in the formation of sterile pustules [14]. Other cytokines, such as granulocyte/macrophage colony-stimulating factor, interferon-γ, and IL-5 (eosinophil-attracting cytokine) are believed to also contribute to the pathogenesis of AGEP [12].

As in other drug-induced cutaneous adverse reactions, if AGEP is suspected, the most important step is the immediate cessation of the causative drug. The patient should be instructed to avoid future use of the culprit medication. Specific therapies that alter the disease course have not been described. AGEP is generally self-limited and symptomatic treatment is recommended. Antipyretics, moist dressings, and disinfecting agents during the pustular stage and moisturizing agents during the desquamation (post-pustular) phase have been recommended for symptomatic relief and prevention of complications such as a secondary infection [1, 15]. It is important to avoid the use of antibiotics unless there is an associated infection. Corticosteroids are generally unnecessary because their benefit in AGEP has yet to be established. However, they can be considered in severe cases.

## Conclusion

Owing to its safety profile, tolerance, and efficacy, cetirizine is used extensively. Therefore awareness of this rare, yet severe adverse reaction induced by cetirizine is imperative. Early diagnosis of AGEP is vital to terminate the exposure to the causative agent and to avoid unnecessary testing and treatment.

## References


1. Sidoroff A, Halevy S, Bavinck JN, Vaillant L, Roujeau JC. Acute generalized exanthematous pustulosis (AGEP)--a clinical reaction pattern. J Cutan Pathol. 2001;28:113-9. [PMID: 11168761]
2. Curran MP, Scott LJ, Perry CM. Cetirizine: a review of its use in allergic disorders. Drugs. 2004;64:523-61. [PMID: 14977391]
3. Calista D, Schianchi S, Morri M. Urticaria induced by cetirizine. Br J Dermatol. 2001;144:196. [PMID: 11167712]
4. Cravo M, Goncalo M, Figueiredo A. Fixed drug eruption to cetirizine with positive lesional patch tests to the three piperazine derivatives. Int J Dermatol. 2007;46:760-2. [PMID: 17614812]
5. Lew BL, Haw CR, Lee MH. Cutaneous drug eruption from cetirizine and hydroxyzine. J Am Acad Dermatol. 2004;50:953-6. [PMID: 15153902]
6. Roujeau JC, Bioulac-Sage P, Bourseau C, Guillaume JC, Bernard P, Lok C, et al. Acute generalized exanthematous pustulosis. Analysis of 63 cases. Arch Dermatol. 1991;127:1333-8. [PMID: 1832534]
7. Bachot N, Roujeau JC. Differential diagnosis of severe cutaneous drug eruptions. Am J Clin Dermatol. 2003;4:561-72. [PMID: 12862499]
8. Sidoroff A, Dunant A, Viboud C, Halevy S, Bavinck JN, Naldi L, et al. Risk factors for acute generalized exanthematous pustulosis (AGEP)-results of a multinational case-control study (EuroSCAR). Br J Dermatol. 2007;157:989-96. [PMID: 17854366]
9. Feind-Koopmans A, Van der Valk PG, Steijlen PM, Van de Kerkhof PC. Toxic pustuloderma associated with clemastine therapy. Clin Exp Dermatol. 1996;21:293-5. [PMID: 8959903]
10. Hanafusa T, Igawa K, Azukizawa H, Katayama I. Acute generalized exanthematous pustulosis induced by topical diphenhydramine. Eur J Dermatol. 2011;21:994-5. [PMID: 21856562]
11. Kumar SL, Rai R. Hydroxyzine-induced acute generalized exanthematous pustulosis: an uncommon side effect of a common drug. Indian J Dermatol. 2011;56:447-8. [PMID: 21965865]
12. Britschgi M, Steiner UC, Schmid S, Depta JP, Senti G, Bircher A, et al. T-cell involvement in drug-induced acute generalized exanthematous pustulosis. J Clin Invest. 2001;107:1433-41. [PMID: 11390425]
13. Bernard P, Lizeveaux-Parneix V, Miossec V, JM B, Drouet M. HLA et prédisposition génétique dans les pustuloses exanthématiques aiguës généralisées (PEAG) et dans les exanthèmes maculo-papuleux (EMP). Ann Dermatol Venereol. 1995;122S38–S9.

14. Schmid S, Kuechler PC, Britschgi M, Steiner UC, Yawalkar N, Limat A, et al. Acute generalized exanthematous pustulosis: role of cytotoxic T cells in pustule formation. The Am J Pathol. 2002;161:2079-86. [PMID: 12466124]
15. Fernando SL. Acute generalised exanthematous pustulosis. Australas J Dermatol. 2012;53:87-92. [PMID: 22571555]