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ORIGINAL ARTICLE

Acute generalized exanthematous pustulosis: A retrospective study of 51 cases in Taiwan

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ABSTRACT

Background/Objective: Acute generalized exanthematous pustulosis (AGEP) is a severe cutaneous adverse drug reaction characterized by fever and numerous sterile non-follicular pustules. It is mainly attributed to drugs, although other factors have been implicated. The objective of this study was to evaluate the clinical and histological features of AGEP in a Taiwanese population.
Methods: In this retrospective study, we reviewed patients diagnosed with AGEP with a EuroSCAR (RegiSCAR) validation score more than 4 (>4, probable to definite cases), between 1992 and 2012 at the Chang Gung Memorial Hospital in Taiwan. Demographic, clinical and laboratory data, pathologic findings, and disease causality were analyzed.
Results: A total of 51 patients were included in this study, with 34 (66.7%) patients being diagnosed with AGEP with drug causality, and 17 (33.3%) patients being diagnosed with AGEP without drug causality. Cases of AGEP with drug causality showed an older average age, and a significantly higher rate of previous drug hypersensitivity history compared to cases of AGEP without drug causality ($p = 0.0018$). None of the patients had a history of psoriasis or had developed psoriasis at the 1-year follow-up. A total of 12 cases (23.5%) had systemic involvement, including liver and kidneys. Penicillin or aminopenicillin (17.6%) and cephalosporins (17.6%) were the most common causative drug groups related to AGEP. In AGEP patients without drug causality, three cases of pathogen infections were identified (1 case of mycoplasma, Coxsackie virus, and Epstein-Barr virus, respectively).
Conclusion: We found that beta-lactam antibiotics were the major drug class responsible for inducing AGEP in a Taiwanese population, but that some infectious pathogens may also contribute to AGEP development.

Introduction

In 1968, Baker and Ryan[1] first reported on five patients with drug-related pustular eruptions of an acute course, who had no history of psoriasis, and the term acute generalized exanthematous pustulosis (AGEP) was later introduced by Beylot et al[2] in 1980. Subsequently, AGEP was better characterized by Roujeau et al[3] and Chang et al,[4] and AGEP is now recognized as a disease entity that is distinct from pustular psoriasis.

AGEP is associated with three main characteristics: (1) an acute generalized formation of numerous, non-follicular, intraepidermal, or subcorneal sterile pustules (<5 mm) on an extensive erythematous background in the absence of bacterial infection, especially on the main flexural folds, as well as on other parts of the body and face; (2) the appearance of neutrophils after T cell infiltration; and (3) the possibility of inducing the dermatologic reaction by patch testing with the corresponding drug. Viral infections,[5] dietary supplements, and hypersensitivity to mercury, radiation, and spider bites[6] have all been reported as possible causes of AGEP; however, approximately 90% of AGEP cases can be attributed to the use of systemic

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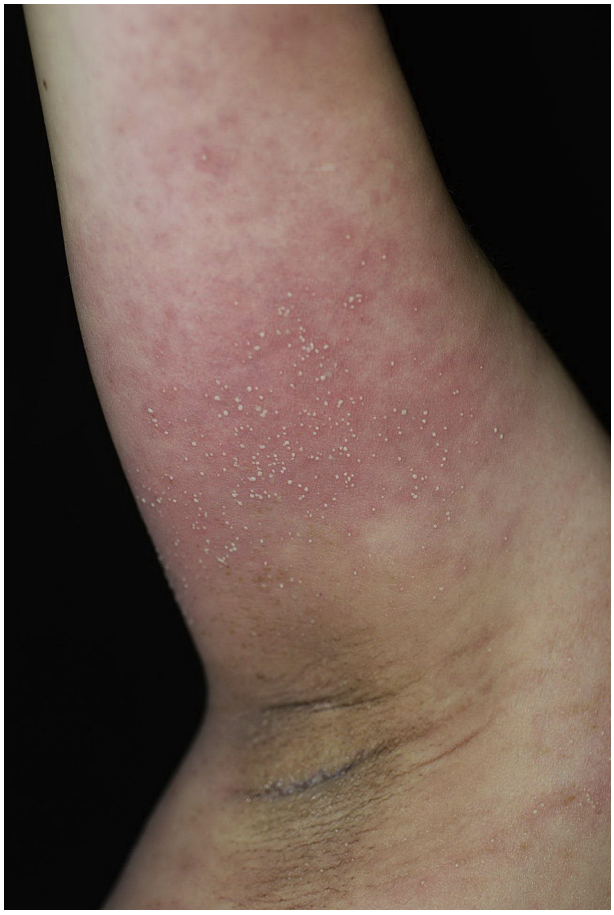

Figure 1 Multiple diffuse erythematous maculopatches studded with several pinpoint, non-follicular pustules with accentuation on the flexural areas in a 34-year-old female patient with drug-induced AGEP.

drugs, especially antibiotics such as aminopenicillin and macrolides.[6] In this study, we reviewed the clinical and laboratory characteristics of 51 patients with AGEP admitted to the Chang Gung Memorial Hospital between 1992 and 2012, to determine the causes of AGEP in a Taiwanese population.

Methods

Patients admitted to the four different branches of Chang Gung Memorial Hospital Health System in Taiwan between 1992 and 2012, and diagnosed with AGEP were analyzed. All cases were assessed by two dermatologists who either evaluated the patients directly, or reviewed photographs, histological data, and clinical information. Information regarding clinical features, laboratory findings, treatment regimens, and medical and family histories was recorded. A diagnosis of AGEP was based on the criteria from the AGEP scoring system established by the EuroSCAR study group.[7] Similarly, criteria for the AGEP validation score were obtained from a multinational European study (EuroSCAR). The AGEP validation score is a standardized scoring system and based on clinical features and histopathology. A patient with an AGEP validation score between 5 and 7 is defined as a probable case, whereas a score between 8 and 12 is defined as a definite case. In this study, we excluded patients with an AGEP validation score <5.

The Naranjo algorithm[8] was used to determine the causality of the suspected adverse drug reactions (ADRs). Briefly, these assessment methods included prior drug reaction history, clinical manifestations of typical drug reactions, chronology or temporal relationship between drug use and onset of reaction, rechallenge, dechallenge, or improvement after discontinuation of suspected drugs, and the notoriety of suspected drugs. The patients were subsequently divided into two groups based on the presence or absence of causative drugs, and the two groups were compared in terms of age, sex, systemic symptoms (such as fever, myalgia, or headaches), duration of disease, history of drug hypersensitivity, and laboratory data.

Results

A total of 51 cases fulfilled the AGEP diagnostic criteria with a validation score >4. Of these patients, 34 cases (66.7%) were identified to have drug causality, whereas 17 cases (33.3%) were not associated with a causative drug (Figures 1 and 2). The mean age of patients with AGEP with drug causality was 53.6 years, which was significantly higher than the age of patients with AGEP without drug causality (30.6 years). No patients in the AGEP without causality group had a history of hypersensitivity. In contrast, 41.2% of

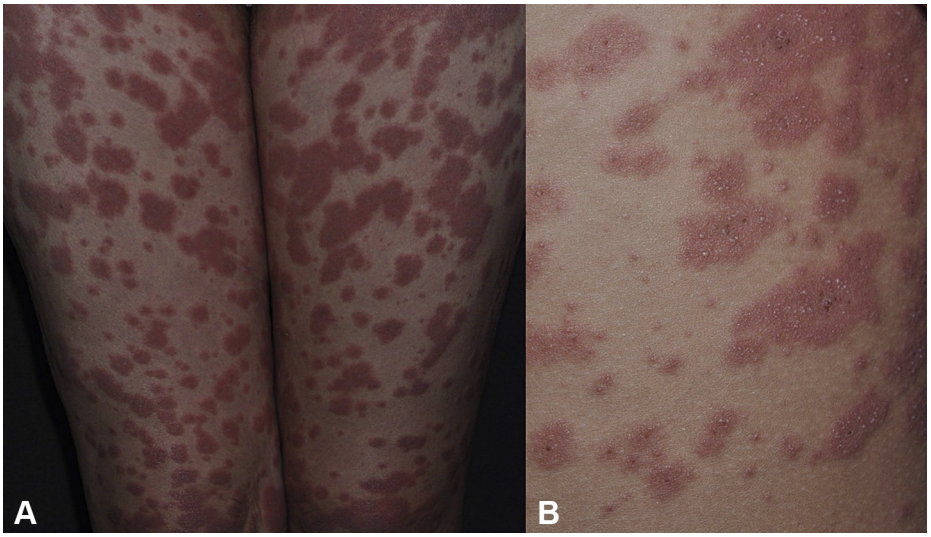

Figure 2 (A) Multiple well-demarcated, erythematous plaques with central purpura on bilateral thighs in a 40-year-old woman diagnosed with AGEP without drug causality. (B) A closer view revealed multiple pustules on the erythematous plaques.

Table 1 Demographic data, disease symptoms, and medical history of AGEP patients with or without drug causality.

	AGEP with drug causality, $n = 34$ (66.7%)	AGEP without drug causality, $n = 17$ (33.3%)
Sex, *n* (%)		
Male	10 (29.4)	5 (29.4)
Female	24 (70.6)	12 (70.6)
Mean age (y)	53.6	30.6
Drug hypersensitivity history, *n* (%)	14 (41.2)	0
Mucosal involvement, *n* (%)	3 (8.8)	4 (23.5)
Disease duration of AGEP, *d*, mean ± SD	10 ± 3.4	10.2 ± 2.6
Occurrence of fever, *n* (%)	28 (82.4)	11 (64.7)
AGEP score, mean ± SD	7.9 ± 1.6	7.7 ± 1.7
Underlying diseases,[a] *n* (%)	22 (64.7)	6 (35.3)
Psoriasis history, *n*	0	0

[a] Underlying diseases included type II diabetes mellitus, hypertension, hyperlipidemia, chronic kidney disease, cancer, and stroke.

Table 3 Pathological findings of AGEP patients with or without drug causality.

	AGEP with drug causality, $n = 28$	AGEP without drug causality, $n = 17$
PMN exocytosis, *n* (%)	25 (89.3)	16 (94.1)
Subcorneal or intraepidermal pustules, *n* (%)	28 (100)	17 (100)
Spongiosis, *n* (%)	14 (50)	9 (52.9)
Dyskeratosis and necrosis of keratinocytes, *n* (%)	4 (14.3)	5 (29.4)
Munro's microabscess, *n* (%)	0 (0)	0 (0)
Psoriasiform hyperplasia, *n* (%)	0 (0)	0 (0)
RBC exocytosis, *n* (%)	1 (3.6)	0 (0)
Papillary edema, *n* (%)	7 (25)	3 (17.6)
Perivascular infiltration, *n* (%)	28 (100)	17 (100)
Leukocytoclastic vasculitis, *n* (%)	0 (0)	1 (5.9)
Capillary dilatation, *n* (%)	3 (10.7)	1 (5.9)
Dermal infiltrates of eosinophils, *n* (%)	9 (32.1)	7 (43.6)

PMN = polymorphonuclear neutrophil; RBC = red blood cell.

AGEP with drug causality cases had previous histories of drug hypersensitivity (0% vs. 41.2%, $p = 0.0018$). A higher rate of comorbidity was found in AGEP with drug causality patients (64.7%), compared to the AGEP without drug causality group (35.3%). Fever, one of the typical symptoms associated with AGEP, was present in 82.4% of AGEP with drug causality patients, and in 64.7% of AGEP without drug causality patients. No patients had either medical or family histories of psoriasis. In addition, none of the patients in this study developed psoriasis during the 1-year follow-up period. The AGEP duration and AGEP score did not differ significantly between the two groups (Table 1).

Beta-lactam antibiotics [penicillin or aminopenicillin (17.6%), and cephalosporins (17.6%)] were the major drugs related to AGEP in this population. Additionally, there were three cases (8.8%) associated with the use of Chinese herbs, and 11 patients had taken multiple drugs before the development of AGEP. Other causative agents included terbinafine, levetiracetam, kanamycin, and lindane. (Table 2).

Neutrophilia and elevated CRP occurred in the majority of AGEP patients in both groups. Eosinophilia was more frequently present in patients with AGEP without drug causality, than in patients with AGEP with drug causality (41.2% vs. 11.8%, respectively, $p = 0.02$). For both groups, blood cultures failed to identify any pathogens. However, three AGEP patients without drug causality were diagnosed with recent Epstein–Barr virus (EBV), Coxsackie virus, and mycoplasma infections, respectively (Table 3). There were a total of 12 cases (23.5%) of AGEP with systemic involvement, including the liver and kidneys. However, only patients with AGEP with drug causality experienced acute renal insufficiency. All patients with systemic involvement showed complete recovery in renal and liver function.

Table 2 Clinical presentations of AGEP patients with or without drug causality.

	Clinical variants		Recruited AGEP, $n = 51$ (%)	
			AGEP with drug causality, $n = 34$ (66.7)	AGEP without drug causality, $n = 17$ (33.3)
Blood dyscrasia, *n* (%)	Neutrophilia[a]		28 (82.4)	16 (94.1)
	Eosinophilia[a]		4 (11.8)	7 (41.2)
	Atypical lymphocytes[a]		4 (11.7)	0 (0)
	Elevated CRP[a]		23 (67.6)	13 (76.5)
	Positive blood culture		0	0
Internal organ involvement, *n* (%)	Hepatitis	1.5 times of ALT[b]	0 (0)	2 (11.8)
		>3 times of ALT[b]	3 (8.8)	3 (17.6)
	Acute renal insufficiency	1.5 times of Cr[c]	4 (11.8)	0 (0)
Causative drugs, *n* (%)	Penicillin or aminopenicillin[d]		6 (17.6)	None
	Cephalosporins[d]		6 (17.6)	None
	Quinolones[d]		4 (11.8)	None
	Multiple drugs		7 (20.6)	None
	Others		8 (23.5)	None
	Chinese herbs		3 (8.8)	None
Identified infectious pathogens[e]			None	Mycoplasma (1), Coxsackie virus (1), EB virus (1)
Atypical distribution	Erythrodermic		1 (2.9)	0

[a] Neutrophilia, value > 7000/μL (normal value < 7500/mL); eosinophilia, value > 700/μL (normal value 50–300/μL); atypical lymphocytes, normal value = 0; CRP, C-reactive protein, normal value range 0–5 mg/L

[b] ALT, alanine aminotransferase, normal value ≤ 40 U/L; mild hepatitis was determined as ALT > 60 U/L, and severe hepatitis was determined as ALT > 120 U/L

[c] Cr, creatinine, normal value range 0.4–1.3 mg/dL; acute renal failure was determined as Cr > 1.8 mg/dL

[d] Penicillin or aminopenicillin included two dicloxacillin and four amoxicillin cases; cephalosporins included three cefazolin, one cefaclor, and two cephalexin cases; quinolones included two ciprofloxacin, one ofloxacin, and one moxifloxacin case; others included one ibuprofen, one vancomycin, one levetiracetam, one terbinafine, one kanamycin, one carbamazepine, one phenytoin, and one lindane case

[e] One case showed anti-mycoplasma IgM of 1178.3 U/mL (normal value < 770 U/mL) and anti-mycoplasma IgG of 2722.9 U/mL (normal value < 100 U/mL); one case showed the anti-coxsackie virus B3 IgM of 130 U/mL (normal value < 30 U/mL); one case showed anti-coxsackie virus B3 IgG of 40 U/mL (normal value < 80 U/mL), anti-viral capsid antigen IgM of 102 U/mL (normal value < 36 U/mL), and anti-viral capsid antigen IgG, 132 U/mL (normal range, < 20 U/mL).

Forty-five patients received skin biopsies, and the most common pathologic findings included exocytosis of polymorphonuclear neutrophils, subcorneal or intraepidermal pustulosis, and spongiosis, which are characteristic for AGEP. Atypical pathologic findings accompanied with pustulosis were also observed in some patients, including dyskeratosis or necrosis of keratinocytes, and lymphocytoclastic vasculitis. No patients presented with Munro's microabscesses or psoriasiform hyperplasia (Table 3).

Discussion

AGEP is a rare condition characterized by sudden eruption of minute, non-follicular pustules on a background of erythema, and is usually associated with fever and neutrophilia. Drug use is the major cause for the development of AGEP. The list of drugs reported is extensive, but certain medications such as aminopenicillins, pristinamycin, quinolones, terbinafine, diltiazem, and antimalarials are associated with a higher risk for AGEP.[4] In this study, we found that beta-lactam antibiotics were the major causative drugs for AGEP in Taiwan.

AGEP patients with drug causality were older and had a higher rate of comorbidity, compared to AGEP patients without drug causality, suggesting that patients in this group might have a higher risk of adverse drug reactions after the use of certain medications. One recent large-scale multinational case-control study (the EuroSCAR study) revealed that some of the most likely drugs to cause AGEP were pristinamycin, ampicillin/amoxicillin, quinolones, (hydroxyl) chloroquine, anti-infective sulfonamides, terbinafine, and diltiazem.[9] In this study, the percentage of patients with identified offending drugs was lower than previous reports. One reason may be that patients in Taiwan frequently take multiple drugs or ingredients, and their drug histories are often difficult to establish. Another potential reason is that patients may have been indirectly exposed to environmental antibiotics or chemical additives, further complicating the identification of AGEP causality.

Eosinophilia is not uncommon in patients with AGEP. Roujeau et al showed in their study that ~30% of AGEP patients had eosinophilia.[3] In our study, 21.6% of all patients presented with eosinophilia. There is still no appropriate explanation for a higher rate of eosinophilia in AGEP patients without drug causality in this study due to limited sample size and without a further investigation; however, potential non-drug antigens such as food additives and environmental residual chemicals could also induce similar AGEP immune reactions and susceptible patients continuously exposed to these environmental antigens without caution may have similar pustular immune reactions.

In this study, we also noted that there were three AGEP cases induced by Chinese herbs. Two of the three patients took herb medication for weight loss, and one of them used the Chinese herbs as food flavoring. An increase in the use of alternative and complementary medicines, such as herbal medicines, has been observed in Chinese society, and it is not surprising that herbal medication can cause AGEP as well as other severe cutaneous adverse reactions, since they are known to contain unsafe levels of heavy metals (including mercury),[10] synthetic drugs, or microorganism contamination.[11]

In addition to drugs, other factors have also been implicated in the development of AGEP, including acute infections with enterovirus, and hypersensitivity to mercury.[3] Similarly, other pathogen infections have been known to contribute to the development of drug hypersensitivity,[12] and infectious pathogen-related AGEP has been reported previously, with known causative agents including enterovirus, cytomegalovirus, EBV, hepatitis B virus, parvovirus B19, *Escherichia coli*, *Chlamydia pneumonia*, *Echinococcus granulosus*, and *Mycoplasma*.[13] In this study, we identified three AGEP patients without drug causality showing recent infections of EBV, Coxsackie virus, and mycoplasma. All our patients of AGEP without drug causality denied insect bite history. As for other infectious pathogens, we did not survey all of them except patients with prodrome or a recent history of suspected viral infections and EBV, HSV, or mycoplasma which are of our routine works for severe drug reactions.

Recently, Hotz et al[14] reported systemic involvement of AGEP in a retrospective study of 58 patients. Systemic involvement, including liver, kidney, bone marrow, and lungs, was observed in 17.2% of their AGEP cases. Comparably, in this study, we found that 23.5% of AGEP cases had systemic involvement, indicating that physicians should be educated and aware of the potential risk of systemic involvement in AGEP.

In conclusion, we demonstrated that drugs, including Chinese herbs, are the main causes for the induction of AGEP in a Taiwanese population. Beta-lactam antibiotics were the major causative drug for AGEP in this population, but some infectious pathogens may also contribute to the development of AGEP. There is potential risk for systemic involvement in patients with AGEP.

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