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

Yung-Yi Lee¹,², Wen-Hung Chung¹,²,*

¹Department of Dermatology, Drug Hypersensitivity Clinical and Research Center, Chang Gung Memorial Hospital, Taipei, Linkou, and Keelung Branches, Taiwan
²College of Medicine, Chang Gung University, Taoyuan, Taiwan

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.

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Introduction

In 1968, Baker and Ryan¹ 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 al² in 1980. Subsequently, AGEP was better characterized by Roujeau et al³ and Chang et al⁴ 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 bites⁶ 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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* Corresponding author. Department of Dermatology, Drug Hypersensitivity Clinical and Research Center, Chang Gung Memorial Hospital, Keelung, Taipei and Linkou Branches, Taiwan.
E-mail addresses: chung1@cgmh.org.tw, wenhungchung@yahoo.com (W.-H. Chung).
drugs, especially antibiotics such as aminopenicillin and macrolides. 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. 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 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...
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 cases, 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.
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, chloroquine, and sulfonamides, are reported to cause AGEP.12 and infectious pathogen-related AGEP has also been reported previously, with known causative agents including enterovirus, cytomegalovirus, EBV, hepatitis B virus, parvovirus B19, Escherichia coli, Chlamydia pneumoniae, Echinococcus granulosus, and Mycoplasma. In this study, we identified three AGEP patients without drug causality showing recent infections of EBV, Coxsackie virus, and mycoplasma. All of our patients of AGEP without drug causality did not have a history of suspected viral infections and EBV, HSV, or mycoplasma which are of our routine works for severe drug reactions.

Recently, Hotz et al14 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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