

Clinical characteristics, culprit drugs and outcome of patients with Acute Generalised Exanthematous Pustulosis seen in Hospital Sultanah Aminah, Johor Bahru

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ABSTRACT

Background: Acute generalised exanthematous pustulosis (AGEP) is a rare, cutaneous reaction characterised by sudden onset of numerous, non-follicular, sterile pustules on oedematous erythematous skin, accompanied by fever and neutrophilia. AGEP is predominantly drug-induced. Skin lesions appear rapidly within 1-3 days of drug exposure and upon drug withdrawal, resolve rapidly within 15 days.

Objective: To determine the clinical characteristics, culprit drugs and outcome of patients with AGEP.

Methods: A retrospective note review of all AGEP patients seen from 2001-2015.

Results: Among 21 AGEP patients, 76% were Malays, 9.5% Chinese, 9.5% Indians, and 5% Iban. Sixteen were females and 5 were males. Median age of patients was 40 years (IQR: 26). The main culprit drug was amoxicillin (10 cases), followed by cloxacillin (three cases), phenytoin (two cases) and one case each of carbamazepine, sulphasalazine, allopurinol, cephalexin, ceftriaxone, celecoxib and herbal product. The median time from drug initiation to onset of AGEP was 3 days (IQR: 5.5). Fever was documented in 52.4%, mucosal involvement 9.5%, purpura 4.7% and blisters 4.7%. Neutrophilia was observed in 63.6% of patients and eosinophilia in 28.5%. While most patients required admission (67%), all achieved complete recovery within 15 days without any sequela.

Conclusions: AGEP predominantly affects Malay females in this study. The most common culprit drug was amoxicillin. Our patients exhibited the classic clinical manifestations of AGEP and confirmed the generally benign nature of this reaction upon drug withdrawal. Although the overall prognosis is good, prompt diagnosis of AGEP is important because drug withdrawal is the mainstay therapy.

KEY WORDS:

AGEP, Acute generalised pustular psoriasis, SCARs, severe cutaneous adverse reactions

INTRODUCTION

Acute Generalised Exanthematous Pustulosis (AGEP) is a rare and severe cutaneous adverse reaction characterised by

sudden onset of numerous pin-point, non-follicular sterile pustules on oedematous erythematous skin. The majority of AGEP are drug-induced.¹⁻¹² Hypersensitivity to mercury and spider bites have also been reported.^{2,8} Other implicated causes included infections namely with parvovirus B19, cytomegalovirus, coxsackie B4 and mycoplasma pneumoniae.^{2,5,8} However, the European study of Severe Cutaneous Adverse Reactions (EuroSCAR) compared 97 cases of AGEP with 1009 normal controls and found no significant association with infection.⁵ The EuroSCAR study identified seven drugs, namely pristinamycin, aminopenicillins, quinolones, hydroxychloroquine, sulphonamides, terbinafine and diltiazem which are highly associated with AGEP.

AGEP can be recognised clinically by the sudden appearance of numerous pin-head sized (<5mm), sterile, non-follicular pustules overlying oedematous erythematous skin, following exposure to an offending drug.¹⁻⁷ The skin lesions typically start on intertriginous areas or face,¹ but is rapidly supervened by widespread distribution. Atypical cutaneous features including purpura, target-like lesions reminiscent of Stevens-Johnson Syndrome, blisters and vesicles have been described.^{1,5} Non-erosive mucous membrane involvement is seen in about 20% of cases, but this is usually mild and confined to one location (mostly oral).¹ The skin manifestations of AGEP are nearly always accompanied by some systemic symptoms, namely fever and neutrophilia. Mild eosinophilia occurs in up to 30% of patients.⁸

Upon drug withdrawal, the pustules rapidly resolve with characteristic pin-point desquamation. Full recovery typically occurs within 15 days and other organs are usually not affected.^{1,9} Reported mortality of 10%-20% among patients with AGEP was mainly due to secondary infections in older patients with multiple comorbidities.^{10,12} In this study, we aim to determine the clinical characteristics, culprit drugs and outcome of AGEP in our population.

MATERIALS AND METHODS

Setting

The department of dermatology in Hospital Sultanah Aminah Johor Bahru keeps a registry of all patients with cutaneous adverse drug reaction (cADR) since 2001. All suspected cADR referred to our department are evaluated by

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a dermatologist before they are registered and reported to our National Drug Monitoring Centre. The first author was one of the dermatologists who routinely evaluated and assessed the causality of drugs implicated in suspected cADR during the study period between January 2001 and December 2015.

Of the 614 patients with cADR (mean age at onset: 41.8 years) seen during the study period, 278 (45.2%) were female. The racial composition of our cADR patients was 62.5% Malay, 28.6% Chinese, 5.8% Indian, and 2.1% others.

Study design and population

This study was done by analysing the ADR reporting forms of patients with dermatologist-diagnosed AGEP who were registered and reported to our National Drug Monitoring centre between January 2001 and December 2015. Patients' clinical notes were traced and counterchecked for any missing or doubtful data. The information gathered included (i) patient demographics (age, gender and ethnicity), (ii) culprit drug(s), (iii) clinical features namely, type of skin eruptions, systemic manifestations, clinical course and outcome.

Our National Drug monitoring centre is a member of the World Health Organization's (WHO) Programme for International Drug monitoring since 1990.¹³ All suspected ADRs in Malaysia were screened by a 12-member Malaysian Adverse Drug Reactions Advisory Committee before they were submitted to the WHO Uppsala Monitoring Centre in Sweden for inclusion into the WHO database. Hence, the WHO causality grading was and is still used to determine the causality of culprit drugs in our national ADR reporting forms.^{13,14} All included patients in this study have a WHO causality grading of at least probable, defined as reasonable time relationship between drug exposure and rash, the event is unlikely to be attributable to concurrent disease or other medicines and a clinically reasonable response is observed on dechallenge. Rechallenge information is not necessary to fulfil this definition.

Patients were also formally scored using the AGEP validation tool developed by the EuroSCAR group² and stratified as to whether their diagnosis of AGEP was possible, probable or definite. The AGEP validation score is a standardized scoring system based on clinical features and histopathology. A patient with an AGEP validation score of between 1 and 4 is defined as a possible case, 5 and 7 is defined as a probable case, whereas a score between 8 and 12 is defined as a

definite case. AGEP score assigned to each included patient was based on consensus among all authors.

Statistical analysis

Descriptive statistics are used to analyse data and presented as counts and percentages for categorical variables. Mean with standard deviation (SD) was used for normally distributed data while median with interquartile range (IQR) was used for data which were not normally distributed. This study was approved by our Institutional Review Board (NMRR-09-560-4282) with exemption from a full ethical review since it was a retrospective study.

RESULTS

Of the 21 patients with AGEP, five (24%) had a definite, six (29%) probable, and ten (47%) possible diagnosis of AGEP based on EuroSCAR scoring system. Sixteen patients (76%) were female and five were male. Median age of patients at onset of AGEP was 40 years (IQR: 26). Among the 21 patients, 76% were Malays, 9.5% Chinese, 9.5% Indians, and 5% Iban.

All patients had generalised erythema studded with characteristic numerous pin-point non-follicular pustules (Figure 1) but mucosal involvement mainly cheilitis and oral mucosa erosions were noted in only two patients. Purpura and blisters were documented in one patient. Fever ($\geq 38^\circ\text{Celsius}$) was documented in 11 (52.4%) patients. Leucocytosis (range 15.7-28.7 $\times 10^9/\text{L}$) with neutrophilia ($\geq 7.5 \times 10^9/\text{L}$) was observed in 63.6% and eosinophilia (range 6% to 19.7%) in 28.5% of patients. Three patients had transaminitis with alanine aminotransferase level of 72, 90 and 162 units/L. Skin swabs and blood culture did not reveal any infection. Only six (28%) patients underwent confirmatory skin biopsies which showed characteristic features of AGEP. (Figure 2).

Three (14%) gave a previous history of drug allergies. Among them, one had a prior amoxicillin-induced AGEP. Nine (43%) had comorbidities. Two patients (9.5%) have concurrent psoriasis and one (4.8%) had pemphigus foliaceus. Other comorbid conditions included hypertension and diabetes mellitus in two patients; hypertension, diabetes mellitus, ischaemic heart disease and cerebrovascular accident (one patient); end-stage renal failure and hypertension (one patient); chronic spontaneous urticarial and asthma (one patient) and allergic rhinitis in another patient.

Table I: Drugs implicated in Acute Generalised Exanthematous Pustulosis (AGEP)

Culprit drugs	No. of patients (%)	Days from drug initiation to onset of AGEP (mean, range)
Amoxicillin	10 (47.6)	2.5 (0.12-7)
Cloxacillin	2 (9.5)	3.5 (1-6)
Phenytoin	2 (9.5)	24.5 (21-28)
Carbamazepine	1 (4.8)	2
Sulphasalazine	1 (4.8)	14
Allopurinol	1 (4.8)	4
Cephalexin	1 (4.8)	1
Ceftriaxone	1 (4.8)	2
Celecoxib	1 (4.8)	7
Herbs	1 (4.8)	1

Table II: Comparison of clinical characteristics of case series on drug-induced acute generalised exanthematous pustulosis

Author (Study period)	This study (2001-2015)	Ainiemi et al ⁹ (1996-2013)	Thienvibul et al ⁹ (2008-2012)	Lee et al ⁴ (1992-2012)	Hotz et al ⁶ (2000-2010)	Choi et al ⁷ (1994- 2008)	Lee et al ¹⁰ (2006-2007)	Guevara-Gutierrez et al ¹¹ (1993-2006)	Tamir et al ¹² (2003-2005)	Roujeau et al ⁸ (NA)
Number of patients, n (year published)	21	28 (25 drug-induced) (2017, USA)	19 (2015, Thailand)	51 (34 drug-induced) (2014, Taiwan)	58 (2013, France)	36 (23 drug induced) (2010, Korea)	8 (2010, Singapore)	12 (10 drug-induced) (2009, Mexico)	13 (2006, Israel)	63 (56 drug-induced) (1991, France)
Age (years), mean (range)	38.3 (7-70)	56 (20-88)	52 (19-84)	53.6 (NA)	53 (19-92)	39.0 (4-80)	63.8 (54-80)	28 (15-56)	46 (22-91)	49.3 (6-85)
Gender, n (%)	5 (23.8%)	11 (39.2%)	9 (47.4%)	10 (29.4%)	24 (42%)	12 (52.1%)	3 (37.4%)	7 (58%)	3 (23%)	30 (47.7%)
Male	16 (76.1%)	17 (60.7%)	10 (52.6%)	24 (70.6%)	34 (58%)	11 (47.8%)	5 (62.6%)	5 (42%)	10 (76%)	33 (52.3%)
Female										
Top 3 culprit drugs (number of cases)	Amoxicillin (10) Cloxacillin (2) Phenytoin (2)	Clindamycin (6) Amoxicillin (3) Cephalexin, cefepime, diltiazem (2 cases each)	Carbapenem (3) Cephalosporin (3) Amoxicillin 2 Omeprazole 2	Penicillins (6) Cephalosporin (6) Quinolones (4)	Amoxicillin (14) Pristinamycin (8) Diltiazem (5) Hydroxychloroquine (3)	Amoxicillin (5) Herbal medication (4) Lacquer (3)	Ceftriaxone (3) Ciprofloxacin, cloxacillin, imipenem, morphine, phenytoin (1 each)	Carbamazepine (4) Cotrimoxazole, Isoniazid, ciprofloxacin, cefalexin, cefotaxime, Phenytoin (1 each)	Acetaminophen (4) Penicillins (2) NSAIDs (2)	Amoxicillin (18) Mercury (8) Ampicillin (5)
Days from drug initiation to AGEP, mean (range)	5.3 (1-28)	8.3 (NA)	NA Median 3 days	NA	NA	9.5 (9-23)	3 (1-6)	2.4 (1-5)	NA	2.5 for antibiotics 18 for other drugs
Fever	52%	36%	52%	82%	NA	NA	100%	92%	92%	92%
Mucosal involvement	2 (9.5%)	3 (11%)	3 (15.8%)	3 (8.8%)	7 (12%)	0	NA	2 (17%)	NA	14 (22.2%)
Neutrophilia	63.6%	88%	68%	82%	73.5%	69.6%	87.5%	92%	76	90.4%
Eosinophilia	28.5%	48%	10%	11%	NA	NA	12.5%	8%	NA	30.1%
Systemic involvement	14.2%	75%	26.3%	23.5%	17.8%	0	0	0	0	32%
Mortality	0	0	0	0	0	0	2	0	1	0



Fig. 1: Amoxicillin-induced Acute Generalised Exanthematous Pustulosis showing characteristic numerous, pin-point, non-follicular pustules on erythematous skin of the abdomen.

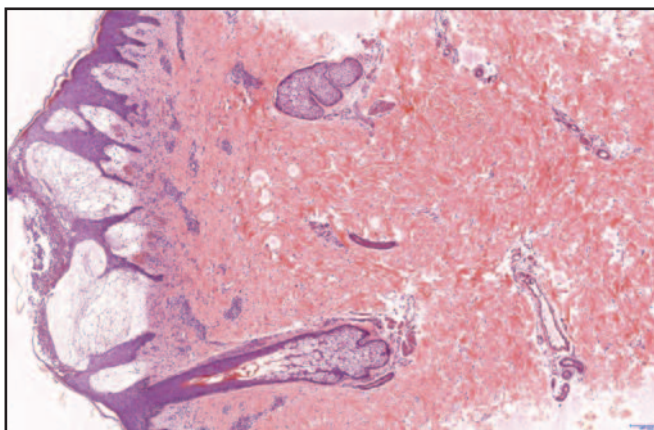


Fig. 2a: Acute Generalised Exanthematous Pustulosis showing characteristic spongiform intra-epidermal micro-abscesses, severe papillary oedema, neutrophil-rich perivascular and interstitial infiltrates with conspicuous eosinophils (Haematoxylin-eosin stain: original magnification X2).

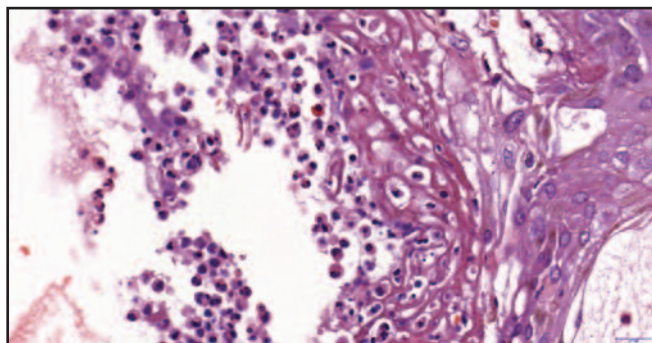


Fig. 2b: Spongiform intra-epidermal micro-abscesses containing characteristic mixed infiltrate of neutrophils and eosinophils, (Haematoxylin-eosin stain: original magnification X40).

We, unanimously, agreed with the initial causality grading of probable or certain relationship of drugs implicated in all 21 reported AGEP during the study period. The distinctive clinical course of AGEP may explain the 100% concurrence rate in the causality assessment of implicated drugs between reporting dermatologists and authors. Table I shows drugs implicated in AGEP. The median time from drug exposure to the development of AGEP was three days (IQR: 5.5). Most of our patients required hospital admission (67%). Eleven patients (53%) were given topical steroids, one (5%) received prednisolone and six (29%) had antihistamines. Pustules settled with characteristic pin-point desquamation within 15 days after drug dechallenge in all patients. Neutrophilia and transaminitis also settled promptly with drug withdrawal. No fatality was documented.

DISCUSSION

Most of our patients with AGEP were female (76%), a finding consistent with the majority of studies with documented female preponderance of between 52% to 76%^{3,4,8,9,12,16} (Table II). The obvious female preponderance is surprising since we have a slight male preponderance in Malaysia and in Johor population of 52.8% males.¹⁵ Furthermore, females only accounted for 45.2% of 614 patients with cADR seen during the study period. Hence, the female preponderance observed is unlikely to be due to differences in health-seeking behaviour between the genders and being female is likely a risk factor for AGEP. Another notable finding is the high proportion of Malays with AGEP (76%) compared to other ethnic groups which comprised of Chinese (9.5%), Indians (9.5%) and Iban (5%). This ethnic distribution, which differed

from Malaysia's general ethnic distribution of 63.1% Malays, 24.6% Chinese and 7.3% Indians suggested variation in risk for AGEP among our multi-ethnic population.¹⁵

The most distinctive feature of AGEP is its clinical course. It has a very rapid onset and equally rapid resolution. Skin lesions appear rapidly within 1-3 days of drug exposure and resolve as rapidly by 5-7 days upon drug withdrawal, followed by pin-point desquamation.¹⁻⁹ The clinical features, course and outcome of our patients with AGEP were as expected of this distinctive cutaneous reaction. Like previous studies, our patients presented with acute onset of characteristic pin-point non-follicular sterile pustules on oedematous erythematous skin (Figure 1), a few days after ingestion of culprit drugs (median duration of 3 days) followed by rapid resolution of AGEP on drug withdrawal without any fatality (Table II). Consistent with previous studies, only a minority of our patients displayed mucosal involvement, mainly cheilitis and atypical lesions namely purpura and blisters.

AGEP is often but not invariably accompanied by fever. Only about 50% of our patients had fever, a finding which is consistent with recent studies from Minnesota, USA and Thailand but contradicts observations of earlier studies from Taiwan, Singapore, Mexico, Israel and France which documented fever in between 80%-100% of patients (Table II). The neutrophilia of 63.6% and eosinophilia of 28.5% observed in our patients are not uncommon among patients with AGEP (Table II). Although only eight patients had biopsies performed, the histologic findings which included i) intra-corneal, subcorneal and/or intra-epidermal spongiform microabscesses containing both neutrophils and eosinophils (Figure 2a & b), ii) papillary dermal oedema and iii) a neutrophil-rich mid-dermal perivascular and interstitial infiltrates admixed with eosinophils are highly characteristic of AGEP and comparable to the key histologic features highlighted by Halevy et al in their analysis of 102 AGEP patients.¹⁶

AGEP has a generally good prognosis although systemic involvement had been reported.^{3,4,6,8,9} Three (14.2%) of our patients had systemic involvement, a finding that concurred with a retrospective review of 58 AGEP patients by Holtz et al., which documented systemic involvement, affecting either renal, liver, bone marrow or lungs, in 17.2% of patients.⁶ Similar to our study, full recovery without mortality was achieved by all 58 patients on drug withdrawal. Outcome was also favourable with no mortality in studies from the USA, Taiwan, Thailand and France which reported systemic involvement in 23% to 75% of AGEP patients.^{3,4,8,9} Although a mortality rate of 10-20% had been documented, it was mainly attributed to secondary infections in elderly patients with multiple comorbidities.^{10,12}

Our data is consistent with previous studies in confirming antibiotics as the most frequently implicated drug group in AGEP (Table II). Amoxicillin, the major offender, was responsible for AGEP in nearly half (47.6%) of our patients. Non-antimicrobial culprit drugs in this study, namely phenytoin, carbamazepine, sulphasalazine, allopurinol¹⁷ and celecoxib¹⁸ have all been previously implicated as causative

drugs in AGEP (Table II). One of our patients developed AGEP after ingesting Habbatus Sauda, an herbal product from medicinal plant *Nigella Sativa*. Herbal medicines are widely believed to be safe although adverse reactions, including life-threatening hepatic and renal toxicity, are not rare.^{19,20} Herbal products were also implicated in studies on AGEP from Taiwan⁴ and Thailand.⁹ Unlike prescription drugs, the content and quality of herbal products are not tightly controlled and contamination with heavy metals including mercury and adulteration with antibiotics are well documented.¹⁹⁻²² Both antibiotics and mercury are associated with AGEP, complicating causality assessment of medicinal herbs in resource poor setting where chemical analysis of herbal products are not readily available. However, chemical analysis of Habbatus Sauda brought by patient was negative for heavy metals and common antibiotics.

Our study is limited by its retrospective nature and the missing clinical data particularly in patients diagnosed before the implementation of point-of-care electronic documentation of clinical notes in November 2004. Another limitation of this study is the small number of patients who underwent skin biopsy. The acute onset of rash and fever following exposure to culprit drugs was readily recognised by patients as drug-induced and rejection of diagnostic skin biopsy is understandable. Unfortunately, histologic features contributed up to 6 points to the EuroSCAR diagnosis of AGEP. Hence, only 53% of our patients satisfied the EuroSCAR criteria for the diagnosis of definite/probable AGEP.

CONCLUSIONS

AGEP predominantly affects Malay females in our study population. The most common culprit drug was amoxicillin. Our patients exhibited the classic clinical manifestations of AGEP and confirmed the generally benign nature of this reaction upon drug withdrawal. Although the overall prognosis is good, prompt recognition and diagnosis of this distinctive adverse cutaneous reaction is important because drug withdrawal is the mainstay therapy.

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