

CLINICAL REPORT

Clinical Manifestations and Characteristics of Patients with Acute Generalized Exanthematous Pustulosis in Asia

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Acute generalized exanthematous pustulosis is a rare, sterile inflammation of the skin (and mucous membranes) characterized by acute onset of generalized pustule formation, fever and leukocytosis, and a rapid resolution. A computer-based search of the literature revealed only a limited series of reports, none of them based on Asian patients. We identified and retrospectively analysed 16 biopsy-proven and criteria-matched patients over a 15-year period in a single medical centre. The study showed a female predominance (11 of 16 patients), a relatively low association with systemic drugs (62.5% vs. 87% in a previous report) and normal renal function (in contrast to a previous report where 32% of patients had renal failure). The study also revealed high levels of C-reactive protein (76.0 mg/l) and normal absolute eosinophil count (176.2/ μ l) in most patients. Furthermore, there was no difference between different treatment regimens regarding the course and duration of the disease or the length of fever ($p > 0.05$). In addition, if the patients were subdivided by aetiology into those strongly associated with or not strongly associated with systemic drugs, a significant difference was found in age of onset between the 2 groups ($p < 0.01$). Key words: acute generalized exanthematous pustulosis; Asians; drug reaction.

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Acute generalized exanthematous pustulosis (AGEP) is a rare, T-cell related, neutrophil-rich, sterile inflammation of the integument (1). The aetiology includes systemic drugs (>90% of cases reported) especially antibiotics such as penicillin and macrolides (2), hypersensitivity to mercury, virus such as enterovirus, contact dermatitis and spider bite (3). Cutaneous manifestations include numerous non-follicular sterile pustules occurring on diffuse, oedematous erythema, especially on the main folds as well as on other parts of the body and face. Fever, neutrophilia, acute onset and rapid resolution are characteristic (2). Mucous involvement may occur in about 20% of cases.

Some criteria have been proposed (2, 4), and a more sophisticated scoring system has been elaborated by the EuroSCAR project (5). A computer-based search (Medline and PubMed) found only a limited series of AGEP, none of which were based on Asian patients (2, 4, 6, 7). The present study is the third largest series on this rare disease, and is the first study of the epidemiological data and clinical features of AGEP in Asian patients.

MATERIALS AND METHODS

Patients

Data were collected from the medical records of patients with AGEP over a 15-year period (1992–2007) in a single medical centre in Taiwan. The review process excluded patients who lacked biopsy-proven lesions or for whom too much clinical or laboratory data were missing. The histopathology of each patient was reviewed and clinical features, laboratory data, treatment regimen, medical history and family history were recorded. All patients fulfilled the characteristics and criteria proposed by Beylot et al. and Roujeau et al. (2, 5), as well as the EuroSCAR scoring system. Finally, 16 biopsy-proven and criteria-matched patients were collected retrospectively and analysed.

The 16 patients were further subdivided in 2 groups according to aetiology. Ten patients belonged to the group strongly associated with systemic drugs and 6 patients had no such association. Factors such as age, time between precipitating factor and onset of skin eruption, drug allergy, duration of disease, fever days, mucosal involvement and laboratory data were compared between the 2 groups.

Statistical analysis

The Mann-Whitney *U* test was used to compare age of onset and other continuous data between the 2 groups, e.g. strongly associated with systemic drugs or not. A χ^2 test was used for ratios such as aetiology and drug allergy, and analysis of variance (ANOVA) to compare different treatment regimens. *P*-values less than 0.05 were considered significant. Statistical analysis was performed using SPSS statistical software.

RESULTS

The patients' ages ranged from 5 to 79 years (mean age 40.9 (SD \pm 26.1) years), and females were predominant (11 of 16 patients). Six of the 16 patients had a history of cutaneous drug reaction, and none of them had a personal or family history of psoriasis. AGEP scores were between 7 and 12 (9.9 \pm 1.2). None of them developed psoriasis in subsequent visits (Table I).

Table I. Characteristics of identified patients with acute generalized exanthematous pustulosis (AGEP)

Patient no.	Age (years)	Sex	Drug allergy history	Neutrophil count (/μl)	Medical history	Possible aetiology	AGEP score	Therapy
1	37	M	No	12,558	Hepatitis, allergy to seafood	Kanamycin	10	Intravenous hydrocortisone
2	27.5	F	Yes	15,010	No	Amoxicillin	10	Intravenous hydrocortisone
3	73	F	Yes	6,272	Hypertension	Carbamazepine	10	Topical steroid
4	40	F	Yes	12,325	No	Cephalexin	10	Intravenous hydrocortisone
5	69	F	No	14,287	Ovarian cancer admission for operation, rheumatoid arthritis	Cefazolin or gentamicin or metronidazole	10	Intravenous hydrocortisone
6	42.5	F	No	14,282	Brain tumour (glioblastoma multiforme)	Phenytoin	7	Intravenous hydrocortisone
7	67	F	Yes	11,012	No	Amoxicillin	11	Intravenous hydrocortisone
8	71	F	No	11,049	Asthma, chronic obstruction pulmonary disease, diabetes	Dicloxacillin	10	Oral methyl-prednisolone
9	79	F	Yes	11,654	Diabetes, hypertension, stroke	Ciprofloxacin	10	Topical steroid
10	61	F	Yes	15,468	Peptic ulcer, rhinitis	Ofloxacin, sulphamethoxazole /trimethoprim, ibuprofen	11	Intravenous hydrocortisone
11	19	F	No	11,625	No	Upper respiratory infection?	9	Oral prednisolone
12	10	M	No	14,960	Recent scabies	Lindane	10	Oral methyl-prednisolone
13	5	M	No	11,760	Allergic rhinitis	Upper respiratory infection?	11	Oral prednisolone
14	11	M	No	13,588	Urticaria for seafood	Gastrointestinal problem?	12	Calamine lotion, antihistamine
15	34	M	No	28,237	Hypertension, gout	Upper respiratory infection?	9	Intravenous hydrocortisone
16	8	F	No	-	No	No contributory causes	8	Oral prednisolone

Onset was acute in patients for whom the condition was strongly associated with systemic drugs, between 3 hours and 7 days after the start of therapy, except for one patient with slow onset up to 30 days after the start of therapy. Three of 6 patients whose condition was not strongly associated with systemic drugs had skin lesions either before or at the same time with infectious symptoms. The duration of AGEP ranged from 4 to 13 days (8.3 ± 2.2 days) and the fever period was between 0 and 7 days. Two of 16 patients had mucosal involvement.

Neutrophilia (93% of available patients, $13,605 \pm 4653/\mu\text{l}$, normal: $< 8140/\mu\text{l}$) and high CRP (100%, 76 ± 65 mg/l, normal: < 5 mg/l) were noted. Absolute eosinophil count ($176.2 \pm 131.6/\mu\text{l}$), renal function (creatinine: 0.8 ± 0.3 mg/dl) and liver function test (alanine aminotransferase: 19.5 ± 13.6 U/l) were generally normal (except for one patient with a slight increase in aminotransferase and one with a history of hepatitis).

The treatment regimens varied: 8 were treated with intravenous hydrocortisone sodium succinate, 5 with oral prednisolone or methylprednisolone, and 3 with topical agents. There was no difference between various treatment regimens regarding course duration (8.5, 8.4 and 7.7 days) and days of fever (3.2, 4.3 and 4.5 days) by ANOVA ($p > 0.05$).

Association with systemic drugs was still the most common aetiology (10 of 16 patients), especially antibiotics, although significantly lower than previously reported (2) (62.5% vs. 87%, $p < 0.05$, χ^2 test). Among the rest of patients, one had contact history with scabicide (8), one had no contributory causes, and 4 had a history of recent infection.

When subdividing the patients by aetiology into those strongly associated with or not associated with systemic

drugs, we found a significant difference in age of onset between the 2 groups (56.7 vs. 14.5 years, $p < 0.01$, Mann-Whitney U test). History of drug allergy was found in 6 of 10 patients in the group whose condition was strongly associated with systemic drugs, while none of the patients in the other group had a history of drug allergy. Differences between the 2 groups for all other parameters, such as time between precipitating factor and onset of skin eruption, duration of disease, fever period, mucosal membrane involvement, C-reactive protein, neutrophil count, alanine aminotransferase, creatinine and AGEP score, were not statistically significant ($p > 0.05$).

Histopathology was typical in all patients. Briefly, all of them had spongiform subcorneal and/or intra-epidermal pustules and some of them had perivascular infiltrates with neutrophils, eosinophils and papillary oedema. None of them had psoriasiform changes.

DISCUSSION

AGEP is a rare disease with features of numerous non-follicular sterile pustules, acute onset, short duration of fever and course, which in majority of cases is related to systemic drug treatment. The pathophysiology is unclear (1, 9, 10). It appears to be a disease where drug presentation elicits a drug-specific CD4+ and CD8+ T-cell activation, and secretion of neutrophil-recruiting factors CXCL8 and GM-CSF, as well as other factors such as interferon- γ , interleukin 4,5 and RANTES. The release of inflammatory cytokines such as interferon- γ may stimulate keratinocytes to secrete CXCL8 and other factors, and T cells are further stimulated by drug-presenting keratinocytes and Langerhans' cells (1, 9). At the same time, CD4+ and CD8+ T cells migrate

to the epidermis and cause the formation of vesicles via tissue destruction by perforin/granzyme B and Fas/FasL-killing mechanism (10). Finally, neutrophils are recruited to the skin and fill the vesicles.

The diagnosis of AGEP is determined on morphology, clinical information, laboratory data and histopathology. Some criteria has been proposed (2, 4), and a more sophisticated scoring system has been elaborated by EuroSCAR project (5). Briefly, the AGEP score is based on morphology, course, and histology. The range of score is between -18 and 12. The differential diagnoses include pustular psoriasis, subcorneal pustular dermatosis, and pustular vasculitis (5). Although most of them can be easily excluded, some may cause problems.

Our study revealed a female predominance, in agreement with one previous report (11), but in contrast to the 2 largest series (2, 6), which showed an equal number of male and female patients. Renal function information was available for 11 patients in our study, and all of them were within normal limits, in contrast to a previous report that 32% (15 of 47 patients) of patients had renal failure (2). Two of 16 patients in our study had mucosal involvement, corresponding to the 20% involvement reported in the previous study, as well as acute onset, short duration, rapid resolution and normal liver function. Our study also revealed high levels of C-reactive protein (76.0 mg/dl) and normal absolute eosinophil count, which were not mentioned previously. One of our patients had onset up to 30 days after starting phenytoin therapy, in contrast to 2.7 days on average if this patient was excluded. This was not surprising, because in drugs other than antibiotics the time between the administration of the suspected drug and the onset of the skin eruption was much longer (18 ± 11 days in a previous report) (2).

Compared with previous reports (2), a relatively low association with systemic drugs was found in this study (62.5% vs. 87%, $p < 0.05$, χ^2 test). Although this may seem surprising, in Stevens-Johnson syndrome, another well-known drug-related reaction, drugs are the cause in only 64% of cases (12). Either the aetiological fraction for drugs in AGEP patients might not be as high as previously thought, or it might be a feature of the Asian population.

Another finding was that the patients with AGEP for whom the causative factor was systemic drugs were much older than these with other aetiologies. The significant difference in history of drug allergy in the 2 groups (6/10 vs. 0/6, $p < 0.05$), might provide some clues. It seems that older patients are more likely to have been previously sensitized by culprit drugs such as antibiotics. Conversely, in the younger group, a heightened immune response (13) might point to minor inciting agents (other than drugs) as potential causes of the reaction. In fact, some authors suggested AGEP might reflect a pattern of immune dysregulation (6). The true explanation for this observation needs to be investigated further.

Due to the self-limited and benign course of this disease, treatment is usually not necessary except for symptomatic therapy and discontinuation of the causative drugs (5). However, most of our patients were commenced on intravenous hydrocortisone, whereas the others were treated with oral prednisolone or methylprednisolone or topical agents alone. We found no difference between different treatment regimens regarding the course and duration of the disease or the length of fever ($p > 0.05$).

Limitations of this study include the small number of cases, which may not represent the whole population, and the retrospective approach, which may be inaccurate in terms of disease and drug history.

The authors declare no conflicts of interest.

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