

Acute generalized exanthematous pustulosis (AGEP) – A clinical reaction pattern

Background: A wide range of diseases or reactions can cause pustular eruptions of the skin. In this spectrum there seems to be a subgroup with characteristic clinical features and a typical course which is mostly caused by drugs for which the term acute generalized exanthematous pustulosis (AGEP) has been established.

Objective: To describe the clinical features of AGEP.

Methods: The authors' experience from a multinational epidemiological study on severe cutaneous adverse reactions and a comprehensive review of the literature were used to provide an overview of the disease and its possible causes. An algorithm for validating cases which was established for this study is also presented.

Results: AGEP typically presents with at least dozens of non follicular sterile pustules occurring on a diffuse, edematous erythema predominantly in the folds and/or on the face. Fever and elevated blood neutrophils are common. Histopathology typically shows spongiform subcorneal and/or intraepidermal pustules, a marked edema of the papillary dermis, and eventually vasculitis, eosinophils and/or focal necrosis of keratinocytes. Onset is acute, most often following drug intake, but viral infections can also trigger the disease. Pustules resolve spontaneously in less than 15 days.

Conclusion: The diagnosis AGEP should be considered in cases of acute pustular rashes and detection of the causative drug should be strived for. Knowledge of the clinical features and usual course of this disease can often prevent unnecessary therapeutical measures.

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When Baker and Ryan described a series of 104 cases of pustular psoriasis in 1968¹ they detected a subgroup of 5 patients who had no history of psoriasis and in which the episode of pustular eruption was very acute, resolved quickly and did not recur. This group was named exanthematic pustular psoriasis and already then the authors suspected drugs and/or infections as trigger for the pustular skin reaction. In the meantime many cases with similar clinical features were described under different denominations such as toxic pustuloderma² and pustular drug rash,³ or were

interpreted as special variants of other pustular diseases. In 1980 Beylot et al.⁴ introduced the term *pustuloses exanthématique aiguës généralisées* (PEAG) to the French literature and its translation acute generalized exanthematous pustulosis (AGEP) is now broadly used in cases of pustular eruptions showing the clinical features discussed below. We will use the term AGEP throughout this paper well aware, that many reported cases of toxic pustuloderma are dealing with the same disease. A clear distinction has to be made from the term *pustulosis acuta generalisata*, which describes a post-



Fig. 1. A) Diffuse erythema in the axilla with hundreds of pustules. B) Close-up view of the same region showing hundreds of small, non-follicular, partially confluent pustules.

streptococcal disease arising mainly in children and different from AGEP.⁵

Clinical features, course, and laboratory findings

Mostly beginning in the intertriginous areas or in the face a diffuse, often edematous erythema develops very acutely. Patients often describe a burning or itching sensation. On this – often widespread – erythema soon dozens to hundreds of small (pinhead sized, 5 mm) non follicular sterile pustules arise mainly in the folds (Fig. 1). Sometimes confluence of pustules may mimic a positive Nikolsky’s sign and thus lead to a misinterpretation as toxic epidermal necrolysis (TEN). Other skin symptoms like marked edema of the face, purpura lesions (especially on the legs), Stevens-Johnson-syndrome-like “atypical targets”, blisters and vesicles have been described but are not typical for AGEP. Mucous membrane involvement may occur in about 20% of the cases but usually is mild and remains limited to one location (mostly oral).

Skin symptoms are almost always accompanied by

fever above 38.5 Celsius and leucocytosis mostly due to blood neutrophil counts above $7 \times 10^9/l$. A mild eosinophilia may be present in about one third of the patients.⁶ Lymphadenopathy has been reported in some cases.⁷ Apart from a slight reduction of the creatinine clearance (< 60 ml/min in 30% of the cases) and a mild elevation of aminotransferases, no involvement of other internal organs has to be expected.

The combination of high fever, leucocytosis and pustules is often misinterpreted as acute infectious disease. Early diagnosis of AGEP is important to avoid unnecessary investigations and/or the administration of expensive and sometimes risky antibiotics.

Pustules resolve spontaneously within a few (4 to 10) days and are – in typical cases – followed by a characteristic postpustular pin-point desquamation (Fig. 2). The overall prognosis is good in AGEP although high fever or superinfection of skin lesions can sometimes lead to life-threatening situations in patients of old age or poor general condition.

Histopathology

The typical histopathology of AGEP shows spongiform subcorneal and/or intraepidermal pustules, an often marked edema of the papillary dermis and perivascular infiltrates with neutrophils and exocytosis of some eosinophils.⁸ Vasculitis and/or some single cell necroses of keratinocytes may be present. Psoriatic changes like acanthosis and papillomatosis are usually absent.⁹

Differential diagnosis

A wide spectrum of cutaneous diseases or reactions can cause pustular eruptions. Most of them can easily be differentiated from AGEP: all follicular eruptions like bacterial folliculitis, furunculosis, acne and acnei-

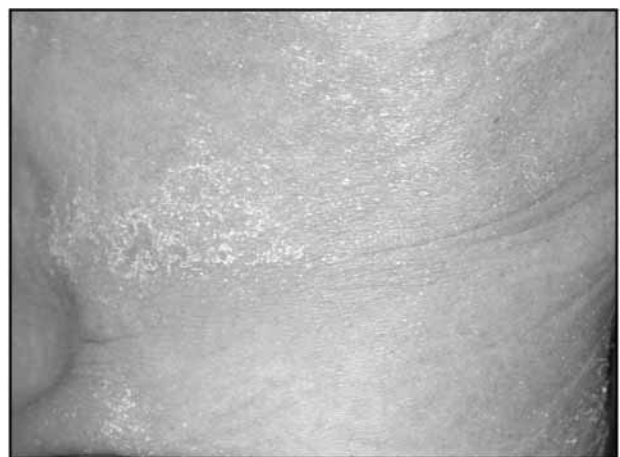


Fig. 2. Typical pinhead-sized postpustular desquamation.

Acute generalized exanthematous pustulosis

form pustules, localized pustular contact dermatitis, dermatophyte infections, pyoderma vegetans, varicella, Kaposi's varicelliform eruption, Sweet's syndrome, impetigo, impetiginized eczema, pemphigus foliaceus and other autoimmune bullous disorders, infantile chronic acropustulosis, migratory necrolytic eruption of glucagonoma, bowel bypass syndrome, Behcet's disease or staphylococcal scalded skin syndrome and others. Yet a couple of diseases remain where differentiation from AGEP may cause problems both, clinically and conceptually.

Pustular psoriasis (von Zumbusch type)

One of the main issues in the discussion whether AGEP (or toxic pustuloderma) is an entity of its own or not is its clinical similarity with pustular psoriasis of the von Zumbusch type, the morphology of the pustules often being indistinguishable in both diseases. Many authors have addressed this issue and until now no clear-cut rules for the differentiation of both entities exist but a list of differences seems to justify the distinction between AGEP and pustular psoriasis (Table 1).

Subcorneal pustular dermatosis (Sneddon-Wilkinson)

Sneddon-Wilkinson disease is characterized by larger, flaccid blisters with hypopyon formation often arranged in a circinate distribution pattern. In addition, evolution of the disease is far less acute than in AGEP.

Pustular vasculitis

Bullous and/or pustular lesions may arise in purpura lesions of leucocytoclastic vasculitis. In addition there seems to be a special variant of leucocytoclastic vasculitis which is characterized by the development of many small pustules which – as opposed to AGEP – are localized mainly on the dorsum of the hands and which might also be drug-induced. A marked leucocytoclastic vasculitis can be detected in histology.^{10,11} Confusion may occur due to the report of some cases

of pustular vasculitis under the term pustulosis acuta generalisata^{5,12} or due to the occasional presence of vasculitis in AGEP.

Drug hypersensitivity syndrome

Drug hypersensitivity syndrome, also referred to as DRESS (an acronym for drug rash with eosinophilia and systemic symptoms) may also show papulo-vesicles and/or papulo-pustules, the pustular component being usually less pronounced than in AGEP. In addition patients show fever, lymphadenopathy, eosinophilia, mononucleosis and often severe visceral involvement like hepatitis, nephritis, pneumonitis, and/or myocarditis.

Toxic epidermal necrolysis (TEN)

The presence of "atypical" target lesions and the confluence of pustules mimicking a positive Nikolsky-sign may suggest the diagnosis of TEN in severe cases of AGEP. In general the distinction can be easily made by experienced physicians as, among other criteria, epidermal detachment in AGEP is much more superficial, and mucous membrane involvement is much more pronounced in TEN. Whereas differentiation in some cases might be difficult on clinical grounds alone, histology is significantly different in TEN typically showing full thickness epidermal necrosis and only a very sparse inflammatory infiltrate. Yet, in our experience even some overlap cases might exist that fulfil the criteria for both diseases both clinically and histologically.

Scoring system

As a conclusion from a retrospective analysis of 63 cases the following five criteria have been suggested for the definition of AGEP: 1) several dozens of small, mostly non follicular pustules arising on a widespread edematous erythema; 2) histopathologic changes as described above; 3) fever ($> 38.3^{\circ}\text{C}$); 4) blood neutrophil counts above $7 \times 10^9/\text{L}$; and 5) acute evolution

Table 1. Differentiation between AGEP and pustular psoriasis

	AGEP	Pustular psoriasis
History of psoriasis	Possible	Mostly
Distribution pattern	Predominance in the folds	More generalized
Duration of pustules	Shorter	Longer
Duration of fever	Shorter	Longer
History of drug reaction	Usual	Uncommon
Recent drug administration	Very frequent	Less frequent
Arthritis	Rare	30%
Histology	Spongiform subcorneal and/or intraepidermal pustules, edema of papillary dermis, vasculitis, exocytosis of eosinophils, single-cell necrosis of keratinocytes	Subcorneal and/or intraepidermal pustules, papillomatosis, acanthosis

Table 2. AGEP validation score of the EuroSCAR study group

Morphology	
Pustules	
Typical*	2
Compatible**	1
Insufficient***	0
Erythema	
Typical	2
Compatible	1
Insufficient	0
Distribution/pattern	
Typical	2
Compatible	1
Insufficient	0
Postpustular desquamation	
Yes	1
No/insufficient	0
Course	
Mucosal involvement	
Yes	± 2
No	0
Acute onset (± 10 d)	
Yes	0
No	± 2
Resolution ± 15 days	
Yes	0
No	± 4
Fever ± 38 °C	
Yes	1
No	0
PNN ± 7000/mm ³	
Yes	1
No	0
Histology	
Other disease	± 10
Not representative/no histology	0
Exocytosis of PNN	1
Subcorneal and/or intraepidermal <i>non</i> spongiform or NOS pustule(s) <i>with</i> papillary edema or subcorneal and/or intraepidermal <i>spongiform</i> or NOS pustule(s) <i>without</i> papillary edema (NOS not otherwise specified)	2
<i>Spongiform</i> subcorneal and/or intraepidermal pustule(s) <i>with</i> papillary edema	3

Interpretation: ± 0: no AGEP, 1–4: possible, 5–7: probable, 8–12: definite.

Remarks: Patients are not included in the study, if only localized pustules are reported, the pustular rash already lasts longer than 3 weeks or a clear alternative diagnosis has been made by a dermatologist.

*Typical: typical morphology as described in the "clinical features" section

**Compatible: not typical, but not strongly suggestive of other disease.

***Insufficient: lesions can not be judged (mostly because of late stage of the disease or poor quality of pictures).

with spontaneous resolution of pustules in less than 15 days.⁶ While performing a multinational epidemiological case-control study on severe cutaneous adverse reactions (EuroSCAR-project) we realized, that these criteria were not precise enough, especially when dealing with the retrospective assessment of cases. We therefore elaborated a more sophisticated scoring system presented in Table 2.

Epidemiology

From the current data males and females seem to be equally affected and AGEP can occur at any age. In one study HLA B51, DR11 and DQ3 were found to be more frequent than in the average population.¹³

Table 3. Anti-infective and non-anti-infective drugs as causes of AGEP

Anti-infectives	References
A) Anti-infectives as causative drugs for AGEP	
β-Lactam antibiotics	4, 6, 8, 18–22
Macrolides	6, 23, 24
Cephalosporins	7, 18, 25–30
Quinolones	31, 32
Tetracyclins	6, 18, 33
Other antibiotics	
Chloramphenicol	3, 34
Gentamycin	35
Imipenem	36
Isoniazid	37
Metronidazol	38
Trimethoprim sulfamethoxazole	39, 40
Vancomycin	6
Antimycotics	
Griseofulvin	18
Itraconazol	41, 42
Nystatin	43, 44
Terbinafine	45–47
Other anti-infectives	
(Hydroxy-)chloroquine	48–52
Diaphenylsulfone	8
Nifuroxazide	53
Pyrimethamine	3
Protease inhibitors	54
B) Non-anti-infective drugs as causes of AGEP (in alphabetical order)	
Agent	References
Acetylsalicylic acid	55
Allopurinol	56, 57
Amoxapine	58, 59
Buphenine	60
Bufexamac	6
Calcium channel blockers	61–64
Carbamazepine	2, 6, 65
Carbutamide	6
Chemotherapy (high dose)	66
Chromium picolinate	67
Cimetidine	8
Clemastine	68
Clobazam	6
Clozapine	69
Dexamethasone	70
Disulfiram	71
Enalapril	18, 72
Eprazinon	73
Fenoterol	74
Furosemide	3
Lansoprazole	75
Nadoxolol	6, 76
Nifedipine	6
Mercury	6, 77, 78
Paracetamol	6, 79, 80
Prostaglandine E1	81
Piperazine ethionamate	3
Pneumococcal vaccine	82
Quinidine	4, 6
Sulbutiamine	6
Sulfasalazine	83, 84
Thalidomide	85, 86
Topical agents	6, 87
PUVA	88

From the inclusion rate in the EuroSCAR study we estimate the incidence rate of AGEP to be in the range of 1 to 5 cases per million per year, but reliable data is missing.

Etiology and pathogenesis

It seems that more than 90% of cases with AGEP or toxic pustuloderma are drug induced. A wide range of drugs has been suspected of causing these reactions in case reports and larger series (Table 3A, B), antibacterials being the most frequent triggers. A high proportion of these cases have been attributed to aminopenicillins or macrolides but interestingly not to sulfonamides, who have a high potential of causing other cutaneous drug reactions. Also an increasing number of cases attributed to antimycotic drugs is being reported. In the group of non-antiinfective drugs especially calcium channel blockers, carbamazepine and paracetamol have been reported as culprit agents in several cases. In a minority of cases viral infections^{6,14-16} have been suspected to trigger AGEP.

After administration of a new drug it may take 1 to 3 weeks until – probably as result of a primary sensitization – skin symptoms arise. Yet there is a second group of patients where the interval between drug intake (especially antibacterials) and skin symptoms may be as short as a few hours to 2–3 days. Such rapid onsets have been described in patients who were rechallenged with the same drug after a first episode of AGEP or patients with a known previous sensitization to topical antibacterials. More often than in other drug reactions patch testing shows positive, sometimes strong and even pustular reactions.¹⁷ Furthermore *in vitro* tests like the macrophage migration inhibition factor (MIF) test and the mast cell degranulation (MCD) test have been shown to be helpful in detecting the causative drugs in AGEP (18). Although the mechanisms of AGEP have not been investigated some of the mentioned features suggest an immunologic recall phenomenon where in particular memory T cells producing neutrophil promoting cytokines like interleukin (IL)-3 and IL-8 play an important role.

Therapy

Obviously the causative drug has to be discontinued and antibiotics are not to be given unless there is a clear and well-documented associated infection. Due to the benign, self-limited course of the disease a specific treatment, especially systemic corticosteroid treatment which is often taken into consideration is usually not necessary. Symptomatically systemic antipyretics can be given if not suspected as causative drug for the disease.

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