Case Reports

Acute generalised exanthematous pustulosis (AGEP)-a potential pitfall for the acute physician

T A Cranga, MA Simpson & P Featherstone

Abstract

Acute generalised exanthematous pustulosis is a rare drug-induced dermatosis with an incidence of 1-5 cases per million cases per year,[1] characterised by the appearance of hundreds of sterile pustules over erythematous and oedematous skin. Fever and neutrophilia are usually present. It has a rapid course and usually resolves following discontinuation of the precipitating drug or as a result of topical corticosteroid treatment.[2,3,4,5] A patient with AGEP, who presented with generalized pustulosis lesions after the use of Flucloxacillin *for* cellulitis is described, along with the management and differential diagnosis of this condition.

Keywords

Drug induced eruption, AGEP

Key points

- AGEP presents with fever, neutrophilia and a rash that could be confused with cellulitis. If mistaken the treatment could become the precipitant of deterioration rather than cure.
- Bilateral erythematous rashes are rarely the result of cellulitis; rashes with unusual distributions should be treated with increased suspicion.

Case History

A 70 year old Caucasian male presented to the Acute Medical Unit (AMU) with an erythematous and pustular rash on both legs as well as fever and neutrophilia. Ten days prior to this presentation, he had seen his GP with a suspected cellulitis of his left leg. He was treated with Flucloxacillin 500mg four times a day. Four days later the rash worsened and the GP,increased the dose of Flucloxacillin to 1g four times a day. The rash progressed, spreading over his trunk and back. He developed a pyrexia and tachycardia and he was referred for admission.

There was no history of psoriasis or any other skin disorders. The patient's past medical history included recurrent episodes of catheter associated urinary tract infections and upper limb weakness from a road traffic accident (1976). Earlier in the month prior to presentation he had been started on warfarin following diagnosis of a Pulmonary Embolism.

His regular medications were Lactulose and Warfarin. He had no known allergies.

On examination, the pustular rash was on a background of widespread erythema with associated tiny exanthematous pustules and desquamation. It was present on the upper and lower limbs, trunk and back but not present on his face, scalp, oral cavity, scrotum or groin. (Figure 1-2) The mucous membranes, palms and soles were also spared. There was no nail involvement.

Nikolsky's sign (a skin finding in which the top layers of the skin slip away from the lower layers when slightly rubbed) was also negative.

The patient's temperature on admission was 38.5°C. Heart rate was 110/min, blood pressure 120/70, and oxygen saturation 94% on 2L O2 via nasal cannulas. His chest X-ray was unremarkable and ECG showed sinus tachycardia. Blood cultures taken on admission remained negative. Urine dipstick was clear. Lactate on admission was 0.9. The rest of the admission bloods are shown in figure 3.

The on-call dermatologist reviewed the patient in the following morning after admission.

The consultant made the clinical diagnosis of florid acute generalised exanthematous pustulosis with neutrophilia (AGEP) secondary to recent course of Flucloxacillin.

The IV antibiotics (Clindamycin-started in A&E on admission) and anti-fungal cream were stopped and he was started on topical steroids (Mometasone QDS) daily as well as Potassium Permanganate 1:10.000 solution and Dermol 500 wash.

Within a week of stopping these medications and being started on topical steroids, the patient's lesions

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Figure 1.



Figure 2.

began clearing and he made a full recovery over 14 days.

Discussion:

Acute generalised exanthematous pustulosis (AGEP) is a severe skin lesion of infectious or drug-related aetiology, characterised by an acute development of a sterile pustular eruption, fever (> 38 degrees centigrade), neutrophilia (more than 7,000 cells/mm3) and specific histology showing intraepidermal or sub corneal pustules.

Antibiotics, mainly B-lactams as well as macrolides, have been implicated in the majority of AGEP cases (in over 90%).[1] Other drugs that have also been involved are antimycotics, tricyclic antidepressant, antimalarial agents, antiarrhythmics, calcium channel blockers.[2,6]

There have been reported cases of AGEP secondary to viral infections (about 5%) such as enterovirus, parvovirus B19, cytomegalovirus, Epstein-Barr, adenovirus, hepatitis B virus as well as hypersensitivity reaction to mercury.[8,9]

The pathogenesis of AGEP is not known. However, there is evidence that there is a T cell mediated reaction with female predominance, involving CD4+T cells, cytotoxic CD8+T cells and inflammatory cytokines. In addition, chemokines produce large amounts of CXCL8, GM–CSF and reduced neutrophil apoptosis.[13,14,15]

The histologic features are characterised by spongiform superficial intra-epidermal pustules, papillary dermal oedema and a polymorphous perivascular dermal infiltrate with eosinophils, and neutrophils.

The histologic differential diagnosis includes pustular psoriasis, pustular dermatosis, contact dermatitis, drug hypersensitivity syndrome and pemphigus.[15]

Most cases are drug related and occur 3-5 days after the commencement of treatment. Commonly, this condition occurs in patients without a previous history of psoriasis or other skin conditions.[2,7,10]

Pustular psoriasis was first described 1968 when Baker and Rya reported 5 cases of pustular psoriasis in patients with no past history of psoriasis.[3,11]

The term AGEP was first introduced in 1980 by Beylot et al. and named in French, pustulose exanthématique aiguë généralisée.[3,12]

Severe drug-induced skin reactions are a major challenge in diagnosis for the non-dermatologist.

AGEP is a rarely encountered disorder that might resemble sepsis. Initially, our patient was treated as a

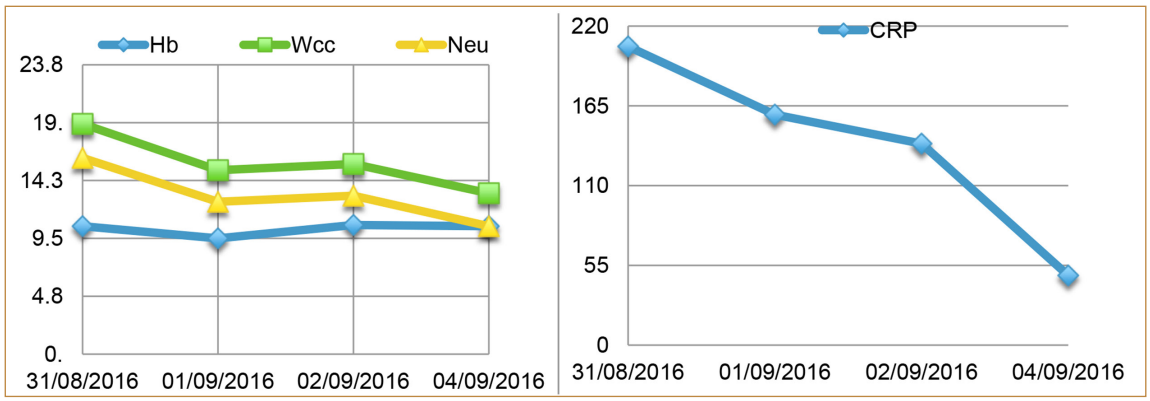


Figure 3. Blood test results

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Table 1. Scoring system of the Euro SCAR study group for acute generalized exanthematous pustulosis.[16,17] The scores obtained by the patient are indicated in the last column.

Criteria	Description	Score	Our Case
Morphology			
Pustules	Typical	+2	+2
	Compatible	+1	
	Insufficient	0	
Erythema	Typical	+2	+2
	Compatible	+1	
	Insufficient	0	
Distribution/pattern	Typical (abdomen, trunk and limbs)	+2	+2
	Compatible	+1	
	Insufficient	0	
Post-pustular desquamation	Yes	+1	+1
	No/Insufficient	0	
Total score			+7
Course			
Mucosal involvement	Yes	-2	
	No	0	0
Acute onset (< 10 days)	Yes	0	0
	No	-2	
Resolution ≤ 15 days	Yes	0	0
	No	-4	
Fever (≥ 38°C)	Yes	+1	+1
	No	0	
Blood neutrophil count (≥ 7000 cells/mm3)	Yes	+1	+1
	No	0	
Total score			+2
Histopathological analysis			
Other diseases		-10	
Not significant/No histology examination		0	0
Polymorphonuclear cell exocytosis		+1	
No subcorneal and/or intraepidermal spongiosis or unspecified, pustule(s) with papilledema or subcorneal and/or intraepidermal spongiosis or unspecified, pustule(s) without papilledema.		+2	
Subcorneal and/or intraepidermal spongiform pustules with papilledema		+3	
Total score			0
Overall score			+9

Note: EuroSCAR= European project dedicated to severe cutaneous adverse reactions. Interpretation: score ≤ 0 indicates no AGEP; 1 to 4 indicates possible AGEP; 5 to 7 indicates probable AGEP; and 8 to 12 indicates definitive AGEP.

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sepsis case with the aforementioned clinical (T>38c) and laboratory (CRP 206, WCC 18.9) findings. After specialist review the diagnosis was excluded by clinical findings and lack of response to IV antibiotics. Early involvement of a dermatologist is essential in the management of this condition.

Non-dermatology specialists and generalists have little confidence in correctly identifying and managing dermatological emergencies, on-call dermatology services are regularly used by other hospital specialists and GPs and are highly valued.

The on-call service aims to reduce morbidity, mortality and reduce the consequences of rare and complex skin disorders by providing clear and efficient service pathways enabling patients to access appropriate expert, patient-centred diagnosis and management.

Our patient demonstrated all the major criteria for AGEP, namely:

1. Numerous, non- follicular pustules on widespread oedematous erythema
2. Post-pustular desquamation
3. Fever >38
4. Neutrophilia
5. Acute symptoms with spontaneous resolution of pustules in less than 2 weeks.

A comprehensive AGEP validation score of the EuroSCAR study group can be used as a diagnostic tool (see table 1). A score between 8 and 12 for AGEP enables a definitive diagnosis.[16,17]

Our patient did not have a skin biopsy but had a score between 8-12 points and this is considered diagnostic for AGEP. Also, a rapid resolution of the condition after interruption of antibiotics, met the criteria for diagnosis.[16,17]

The most important step in the success of the treatment is to discontinue the offending agent.

In our case, oral anti-inflammatory and topical treatments were sufficient to achieve the desired response, characterised by postpustular desquamation.

This patient did not require systemic steroids, although there are some cases described in the literature where systemic steroids are used in AGEP. In studies where systemic steroids were used, there was no standard dose and the benefit remains unclear, as the time to resolution was longer than for topical steroids.[8]

A wide spectrum of cutaneous diseases or skin reactions can cause similar pustular eruptions, which should be differentiated from AGEP: furunculosis and follicular eruptions like bacterial folliculitis, localized pustular contact dermatitis, varicella and Kaposi's varicelliform eruption, impetigo eczema, some autoimmune bullous disorders such as pemphigus foliaceus, Bechet's disease and others.[18]

Some diseases may cause particular problems in differentiation from AGEP:

Pustular psoriasis

The acute generalized type is also termed von Zumbusch variant. This form of pustular psoriasis is accompanied by fever and toxicity, and it may be fatal if proper supportive measures are not taken during the acute phase. The morphology of the pustules may be indistinguishable in both diseases. AGEP is associated with IL36RN mutations similar to those found in pustular psoriasis, palmoplantar pustulosis, and acrodermatitis continua of Hallopeau, which is not surprising given the similarities in clinical and immunologic features of these diseases. Taken together, some dermatologists consider AGEP a drug-induced form of pustular psoriasis.[19]

Pustular vasculitis

Pustular cutaneous vasculitis results from a heterogeneous goup of disorders, characterized by pustules on purpuric bases. Although the cause of this group of conditions is diverse, the histopathologic picture of the lesions is the same, showing a leukocytoclastic vasculitis. Confusion may occur due to the report of some cases of pustular vasculitis (pustulosis acuta generalisata) or due to the occasional presence of vasculitis in AGEP.[20,22]

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 some severe cases of AGEP.

Drug hypersensitivity syndrome (DRESS)

Drug rash with eosinophilia and systemic symptoms syndrome is a severe idiosyncratic drug reaction with a long latency period. This syndrome causes a diverse array of clinical symptoms, anywhere from 2 to 8 weeks after initiating the offending drug, the pustular component being usually less pronounced than in AGEP. This condition can often be complicate by severe visceral involvement, e.g. hepatitis, nephritis, pneumonitis, or myocarditis.[20]

Declaration of competing interests

Nothing to declare.

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