



ACUTE GENERALIZED EXANTHEMATOUS PUSTULOSIS INDUCED BY SIMVASTATIN

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Abstract. Acute generalized exanthematous pustulosis is an acute pustular eruption occurring most commonly after drug ingestion. It is a self-healing condition with spontaneous cure after discontinuation of the causative drug. We report the second case, as far as we know, of acute generalized exanthematous pustulosis induced by simvastatin intake. Conclusion: simvastatin can be included on the long list of AGEP inducing drugs.

Keywords: statins, simvastatin, AGEP, drug eruption

Introduction

Acute generalized exanthematous pustulosis (AGEP) is a rare skin eruption, associated principally with drugs. Antibiotics, particularly β -lactams and macrolides have been implicated in the majority of AGEP reported cases. Other drugs that have also been involved are: antimycotics, analgetics, antipyretics, antimalarial agents, antiarrhythmics, tricyclic antidepressants, calcium channel blockers. There is a growing list of other drugs in the literature that can lead to AGEP. Occasional cases of AGEP have been attributed to viral infections (enterovirus), hypersensitivity to mercury, contact dermatitis, UV exposure [1,2].

AGEP is considered to be a clinical and histological entity with distinctive characteristics. Roujoau et al. proposed some diagnostic criteria for AGEP as a conclusion from a retrospective analysis of 63 cases:

1. The appearance of numerous small pustules of less than 5 mm, the majority non-follicular on a generalized edematous erythema associated or not with purpura and a target aspect
2. Histopathologic study showing intraepidermal or subcorneal pustules associated with the following findings: dermal edema, vasculitis, perivascular

infiltrate rich in eosinophils or focal necrosis of keratinocytes.

3. Fever higher than 38°C
4. Blood neutrophil counts above $7 \times 10^9/L$
5. Acute evolution with spontaneous resolution of pustules in less than 2 weeks.[1]

Ten years later, after performing a multinational epidemiological case control study on severe cutaneous adverse reactions (EuroSCAR-project) Sidoroff et al. propose a new sophisticated scoring system for AGEP diagnosis, presented in table I. (2001, *J Cutan Pathol*)

Case report

In this article we present the second case, as far as we are aware, of AGEP induced by statins treatment.

A 67-old man was admitted to hospital with an extensive erythematous and pustular eruption of sudden onset associated with fever (a temperature of 38.9°C) and malaise. The lesions started on the face and neck and later spread to the rest of the skin. The palms and soles were not affected. It had no mucous membrane involvement. No lymphadenopathy. The patient complained of itching.

The laboratory revealed a total white blood cell count of $13.8 \times 10^9/L$ with 75.5% neutrophils. Inflammation markers, fibrinogen, CRP and ESR values were also raised. The pustule was sterile. Serum

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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 days)	
Yes	0
No	-2
Resolution <15 days	
Yes	0
No	-4
Fever >38°C	
Yes	+1
No	0
PNN >7000/mm³	
Yes	+1
No	0
HISTOLOGY	
Other disease	-10
Not representative/no histology	0
Exocytosis of PNN	+1
Subcorneal and/or intraepidermal non spongiform or NOS pustule(s) with papillary edema or subcorneal and/or intraepidermal spongiform or NOS pustule(s) without papillary edema (NOS=not otherwise specified)	+2
Spongiform subcorneal and/or intraepidermal pustule(s) with 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 cannot be judged (mostly because of late stage of the disease or poor quality of pictures).(2)	

Table I. AGEP validation score of the EuroSCAR study group

renal and liver function tests were within normal limits. He received symptomatic treatment with antipyretics and antihistaminics. The symptoms resolved spontaneously within 2 weeks and residual shedding was observed.

The patient had a known history of psoriatic arthritis which responded very well to NSAIDs. He had a mild form of cutaneous lesions and in the moment of skin eruption he was not receiving any treatment for those lesions, only emollients.

On the onset of skin eruption the patient was

on treatment with systemic medications for different diseases: simvastatin for hypercholesterolemia, meloxicam for arthritis and enalaprilum for arterial hypertension.

The rapid onset and the clinical aspects brought us the idea of drugs skin eruptions, particularly AGEP. All systemic medications were stopped.

In this case, the validation score proposed by Sidoroff et al. based on rash morphologic and histological characteristics and disease course, indicated a definite diagnosis (score >8).

The major differential diagnosis is acute pustular psoriasis (von Zumbusch type). Rapid resolution, pustules predominantly on folds, no recent exposure to corticosteroids but other drugs, exclude this possibility. Other differential diagnosis options are erythema multiforme but no target lesions, subcorneal pustular dermatosis (Sneddon-Wilkinson), Sweet syndrome, TEN and pustular vasculitis.

The histopathologic characteristics of early AGEP lesions are papillary edema, neutrophil clusters in the dermal papilla and perivascular eosinophils, whereas advanced lesions show intraepidermal or subcorneal spongiform pustules.

It is important to identify the precise drug that caused this skin eruption. Patch test can be one solution for that purpose. Our patient had a mild erythema only to simvastatin after patch test application. Positive patch test can sustain the diagnosis but negative results cannot deny it. The sensibility of patch test is only 50%.

One month later the patient returned to his basic treatment for psoriatic arthritis and no skin eruption was observed.

Discussions

AGEP was first described by Roujeau and Bioulac-Sage [1]. It usually has a sudden onset affecting intertriginous areas or the face as a diffuse, edematous erythema associated with small, non-follicular sterile pustules [2,4]. Fever and leukocytosis mostly with neutrophils are always present. AGEP is a self healing condition that resolves spontaneously with the discontinuation of the causative drug [3].

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 [2].

The mechanism of AGEP is not very well proven but it is considered to be an autoimmune reaction with specific T cells playing a crucial role. They produce a large amount of neutrophil attracting cytokines such as IL3 and IL 8 [2]. IL 5 can also be elevated, this explaining the eosinophilia met in some cases [5]. Britschgi et al. consider AGEP as

a reaction where a cell bound drug presentation elicits specific CD4 and CD8 immune response which results in elevated IL8 expression [9]. Keratinocytes seem to play an important role in the pathogenesis of this disease, because they express cytokines which attract PMNs and eosinophils [5].

It has been suggested that specific CD4+ T cells and probably CD8+ cells are the first to react and may be responsible for the formations of vesicles. PMNs migrate later to fill the vesicles and transform them into pustules [5].

Moreau et al. propose that AGEP is a delayed type of hypersensitivity reaction. Another possible mechanism is the production of antigen-antibody complexes induced by an infection or drug that activate the complement system, which in turn leads to neutrophil chemotaxis [4].

Because oral rechallenge tests are not ethical and have the potential to produce generalized eruption even at low doses, the patch test is an alternative to prove the role of a suspected drug and it is particularly useful when there may be several causative drugs. Although its sensitivity is about 50% and negative tests do not allow a final conclusion, positive results are of great value [3].

Our patient displayed the classic features of AGEP with characteristic morphology, histology and course. It is the second case reported about AGEP induced by simvastatin.

The other case, reported by T. Oskay and L. Kutluay, was a 57 year-old man in treatment with zocor 20 mg/day for two weeks after the beginning of skin eruption [7].

We concluded that HMGC_oA can be added to the list of potential causes of AGEP.

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