Accepted Date : 26-Jul-2010
Article type : Original Article

THE SPECTRUM OF HISTOPATHOLOGICAL FEATURES IN ACUTE GENERALISED EXANTHEMATOUS PUSTULOSIS: A STUDY OF 102 CASES

S. Halevy[1] MD, S. H. Kardaun[2] MD, B. Davidovici[1] MD,

J. Wechsler[3] MD, for the EuroSCAR and RegiSCAR study group
[1] Department of Dermatology and Venereology, Soroka Medical Center,
Faculty of Health Sciences, Ben-Gurion University of the Negev, Beer-Sheva, Israel.
[2] Department of Dermatology, University Medical Center Groningen,
University of Groningen, Groningen, the Netherlands.
[3] Department of Pathology, Henri-Mondor Hospital, Faculty of Medicine, Paris XII University, Creteil, France

Running head: Histopathological features in AGEP

Keywords:
Acute Generalised Exanthematous Pustulosis; AGEP; Cutaneous Adverse Drug Reaction; Histopathology

E-mail addresses:
halevy@bgu.ac.il; s.h.kardaun@derm.umcg.nl; bdavidovici@yahoo.com; jwechsler@noos.fr

Corresponding author:
Sylvia H. Kardaun, MD
University Medical Center Groningen, dept. Dermatology
Hanzeplein 1, 9713 GZ Groningen, The Netherlands.
Tel +31 50 3612520
Fax +31 50 3619247
(s.h.kardaun@derm.umcg.nl)

Previously presented as:
1. Halevy S, Kardaun S, Davidovici B, Wechsler J. Histopathology of the skin in Acute generalized Exanthematous Pustulosis (AGEP) – A study of 102 cases. 6th Annual European Society for Dermatological Research Meeting, September 7-9, 2006, Paris, France. The Journal of Investigative Dermatology 2006;126, (Suppl. 3):114s (Abstract # 671)
2. Halevy S, Kardaun S, Davidovici B, Wechsler J. Histopathology of the skin in Acute generalized Exanthematous Pustulosis (AGEP) – A study of 102 Cases. 32th Annual Meeting of the Israel Society of Dermatology and Venereology, June 18-19, 2008, Tel-Aviv, Israel. (Abstract Book)

Funding/Support:
The EuroSCAR study was funded by the following institutions/companies: ADIR & Cie, Bayer Pharma / AG / Vital, Boehringer Ingelheim, Cassenne, Ciba Geigy / Novartis, Cilag GmbH, Dr. Willmar Schwabe, Goedecke Parke Davis, Glaxo Wellcome / GlaxoSmithKline, Hoechst AG / Hoechst Marion Roussel / Aventis, Hoffmann-La-Roche, IRIS Servier, Jouveinal Lab., LEO, LILLY, MSD Sharp & Dohme, Pfizer, Rhone Poulenc Rorer, Sanofi Winthrop / Sanofi Synthelabo GmbH , Schering AG. Funding from Pharmaceutical Companies in France was managed through contract with INSERM (Institut National de la Santé et de la Recherche Médicale), French Ministry of Health (PHRC AOM 98027). The German Registry (the basis for EuroSCAR in Germany) was funded in part by the Federal Institute for Drugs and Medical Devices (BfArM).
The RegiSCAR study was funded by grants from the European Commission (QLRT-2002-01738), GIS-Institut des Maladies Rares and INSERM (4CH09G) in France, DFG (FOR 534) in Germany and by a consortium of Pharmaceutical companies (Bayer Vital, Boehringer-Ingelheim, GlaxoSmithKline, MSD Sharp and Dohme, Merck Novartis, Pfizer, Roche, Sanofi-Aventis, Servier).

Role of the Sponsors: The sponsors had no role in the design or conduct of the study, in the collection, analysis, and interpretation of data, or in the preparation, review, or approval of the manuscript.

Financial Disclosure: "None reported."

Acknowledgment: We are indebted to all SCAR-patients and all the collaborating hospitals and colleagues for their important contribution to this work.
The authors also thank the following EuroSCAR and RegiSCAR principal study investigators for their important contributory comments and assistance: Prof. Jean-Claude Roujeau, Department of Dermatology, Henri Mondor Hospital, Paris XII University, Créteil, France; Mrs. Peggy Sekula, Institute of Medical Biometry and Informatics (IMBI), University Medical Center Freiburg, Freiburg, Germany; Mrs. Ariane Dunant, Biostatistics and Epidemiology Unit, Institut Gustave-Roussy, Villejuif and Reference Center for Toxic and Autoimmune Blistering Diseases, Department of Dermatology, Henri-Mondor Hospital, Paris

What's already known about this topic?

- Knowledge of the histopathology of AGEP is based primarily on case reports and a few clinical studies.

What does this study add?

- The present study includes a large collection of validated AGEP cases that were collected in a systematized manner within two international studies. The histopathological evaluation of AGEP was based on a standardised grading system. The paper shows the prevalence of the various histopathological criteria and provides unique diagnostic clues that support the diagnosis of AGEP.

SUMMARY

Background: Acute Generalised Exanthematous Pustulosis (AGEP) is a rare severe pustular reaction pattern with a typical clinical picture.

Objectives: To characterise the histopathological features of AGEP in a large series of cases with a validated diagnosis.

Patients and methods: A multi-national retrospective histopathological study was conducted. It included 102 hospitalised patients (recruited within the EuroSCAR and RegiSCAR studies) with a validated diagnosis of probable or definite AGEP. A systematic description of the histopathologic features in AGEP was done based on a standardised grading system.

Results: Sub/intracorneal pustules (41%), intraepidermal pustules (20%) or combinations of them (38%) were observed in 102 cases. The pustules were usually large (>15 keratinocytes) (82% and 89%, respectively) and regularly contained eosinophils (36% and 32%, respectively). Spongiform features were less prominent in the sub/intracorneal pustules compared to the intraepidermal pustules (44% and 95%, respectively). The main epidermal features were necrotic keratinocytes (67%), including incidental segmental necrosis (7%), and spongiosis (80%) with neutrophil exocytosis (77%). The main dermal features were papillary oedema (88%) and mixed superficial (100%), interstitial (93%), and mid/deep-dermal infiltrates (95%) containing neutrophils (100%) and eosinophils (81%). Follicular pustules were also seen (23%), but vasculitis generally was absent. Classical features of plaque-type psoriasis were infrequent and usually mild. No significant differences were observed between a sub-group of 16 cases with and 86 cases without psoriasis.

Conclusions: The present histopathologic study concerns a large series of cases with a validated diagnosis of AGEP. It provides diagnostic clues in favour of AGEP in patients with a pustular eruption.

INTRODUCTION

Acute generalised exanthematous pustulosis (AGEP) is a rare, severe, acute-onset pustular reaction pattern characterised by a typical clinical picture and course. AGEP is attributed mostly to drugs, although other etiologies such as viral infections due to human parvovirus B19, cytomegalovirus, and Coxsackie B4, hypersensitivity to mercury and spider bite have been implicated.[1-12]

Clinically, AGEP is characterised by the sudden appearance of dozens of sterile, non-follicular pinhead sized pustules arising on oedematous erythema with a predilection to the big folds, or widespread distribution. Mild, non-erosive mucous membrane involvement (mostly oral) may occur in about 20% of the cases. Other skin symptoms, such as marked oedema of the face, purpura, "atypical target-like lesions" and blisters have been described but are not typical for AGEP. The course of AGEP is characterised in most of the cases by fever (≥ 38°C) and elevated blood neutrophil count (≥ 7000/μ/L). Mild eosinophilia may be present in about one third of the patients.[13] Pustules resolve spontaneously within a few days, followed typically by post-pustular, pin-point desquamation. The reaction resolves fully in ≤ 15 days. Internal organs are generally not involved and the disease has a favourable prognosis, although secondary infection might pose a danger to patients in poor general medical condition. The reported mortality is 5%.[14]

Eruptions similar to AGEP have been described in the literature as toxic pustuloderma or pustular drug eruption,[15-21] or have been interpreted as special variants of other pustular diseases, such as exanthematic pustular psoriasis (PP), suspected to be triggered by drugs or infections.[22,23]

Knowledge of the histopathology of AGEP is based primarily on case reports and a few clinical studies.[1,3,4,13,24-29]

The aim of the present study was to characterise the histopathological features in a large series of cases with a validated diagnosis of AGEP.

PATIENTS AND METHODS

Source of patients

The AGEP patients came from two multi-national studies devoted to Severe Cutaneous Adverse Reactions (SCAR): The EuroSCAR study, conducted in France, Germany, Italy, the Netherlands, Austria, Spain and Israel during the years 1997-2001[2,30] and the RegiSCAR study, conducted in France, Germany, Italy, the Netherlands, Austria and Israel since 2003.[31,32] In both studies AGEP cases were actively detected in a network of hospitals in Europe and Israel. Potential AGEP cases were patients admitted to hospital due to acute pustular skin reactions (i.e. community cases) or who developed such reactions during a hospital stay (i.e. hospital cases). They had dozens of pustules that could not be attributed to another definitive diagnosis. All patients signed informed consent to participate in those studies. The study was approved by the Helsinki Committee of each participating center that recruited patients.

Case validation

An international committee of experts validated the diagnosis of AGEP based on a special standardised scoring system that was developed in the EuroSCAR study, the AGEP validation score.[2,33] Based on the score, patients were either excluded from the study or classified as definite, probable or possible cases.

Inclusion of cases

The present study population was comprised of patients with a definite or probable diagnosis of AGEP and a skin biopsy with slides available for histopathological investigation.

Histopathologic evaluation

The histopathological study was performed on haematoxylin-eosin (HE) stained sections.

All four readers viewed the same slide with a multi-headed microscope and discussed it together at that time. When several sections were available for a particular patient only the most informative specimen was chosen, based on the proper representation of the epidermis and dermis and the presence of an acute inflammatory process, preferentially including a pustule. When several pustules were present in a section, the largest was evaluated.

Evaluation was based on a standardised list of histopathological parameters used for the diagnosis of AGEP. A severity scale of the various histopathological parameters, ranging from 0 to 3 was developed (Table 1), and the degree of severity was determined by consensus.

Analysis and statistics

Data were analysed using SPSS (version 12, SPSS, Chicago, IL). The frequencies of different variables in two subgroups (with and without a background of psoriasis) were compared using the t-test for continuous variables, or the chi-square or Fisher's exact test for differences in proportions, as appropriate.

RESULTS

The present study included 102 cases with a definite or probable diagnosis of AGEP: 86 of 134 cases from the EuroSCAR study and 16 of 70 cases from phase I of the RegiSCAR study (cases enrolled in the study until the end of 2004). Seventy cases (68.6%) originated from France, 22 (21.6%) from Israel (see reference no. 5 for the clinical profile of nine cases), and 10 (9.8%) from the Netherlands. A personal history of psoriasis was recorded in 16 cases (15.6%) (11 from the EuroSCAR study and five from the RegiSCAR study).

The skin biopsies were taken from a known clinical lesion in only 45 of the 102 cases (44%): 40 biopsies (39%) were obtained from pustules (sometimes associated with erythema, oedema, or purpura) and five (5%) from non-pustular clinical lesions, described as erythema or oedema.

The prevalence rates of the broad range of histopathological parameters seen in the 102 cases are presented in Table 2. Pustules were found in 94 cases (92%) and the location of the pustules was sub/intracorneal in 41%, intraepidermal in 20%, and combined in 38%. In addition to subcorneal pustules, subcorneal pustules contiguous with intracorneal pustules, and intracorneal pustules were also seen. The intraepidermal pustules were located in the upper part of the epidermis, most often contiguous with subcorneal or sub/intracorneal pustules. The sub/intracorneal and intraepidermal pustules were usually large (>15 keratinocytes) in 82% and 89%, respectively, and regularly contained eosinophils (36% and 32%, respectively). Spongiform features were less prominent in the sub/intracorneal pustules compared to the intraepidermal pustules (44% and 95%, respectively). Follicular pustules were seen in 22 cases (23%). They were accessory, predominant, or alone. The main epidermal features (Figures 1, 2, 3) were necrotic keratinocytes (67%) including segmental necrosis (7%), and spongiosis (80%) with neutrophil exocytosis (77%). The main dermal features were papillary oedema (88%), mixed superficial (100%), interstitial (93%), and mid/deep-dermal infiltrates (95%) containing neutrophils (100%) and eosinophils (81%). Erythrocyte extravasation (54%) was also observed, but vasculitis occurred only once (1%). Classical features of plaque-type psoriasis were infrequent and usually mild. These included the presence of Munro abscesses (17%), parakeratosis (62%), suprapapillary plate thinning (7%), tortuous and dilated blood vessels (16%), and absence of the granular layer (3%). The calculated mean mitosis was 0.95/high-power field at magnification x40.

Three levels of prevalence were observed. All AGEP cases showed superficial infiltrates (mostly moderate) and dermal neutrophils (mostly scattered). Additional features observed in 80-99% of AGEP cases were large sub/intracorneal or intraepidermal pustules, spongiform intraepidermal pustules, spongiosis (mostly mild), papillary oedema, mid/deep-dermal infiltrates (mostly discrete), interstitial infiltrates (mostly discrete to moderate), dermal

eosinophils (usually just a few), absence of vasculitis, presence of granular cell layer, rete ridges fusion (mild to moderate), and absence of classical features of plaque-type psoriasis (Munro abscesses, suprapapillary plate thinning, tortuous and dilated blood vessels, and a high mitotic rate). Additional features observed in 50-79% of AGEP cases were necrotic keratinocytes, parakeratosis, extravasation of erythrocytes, exocytosis of neutrophils (usually just a few), rete ridge elongation (mild to moderate), and clubbing (mostly mild).

There were no statistically significant differences in the prevalence of histopathological parameters between a sub-group of 16 AGEP cases (15.6%) with a personal history of psoriasis and the 86 AGEP cases with no personal history of psoriasis (data not shown).

DISCUSSION

The present study, which focused on the histopathological evaluation of AGEP, included unique features in design and methodology: a) the study population consisted of patients recruited in two multi-national studies with a validated diagnosis of probable or definite AGEP; b) validation of the diagnosis was based on a special standardised scoring system, the AGEP validation score;[2,33] c) it included the largest series of AGEP cases; d) the histopathological evaluation of AGEP was based on direct investigation of the slides by four investigators using a multi-headed microscope; and e) evaluation was based on a standardised grading system related to pustules, epidermis, dermis, and psoriasis-like changes developed by the authors.

The main histopathological findings, in a previous clinical study of 63 cases of AGEP[13] with 64 biopsies from 48 patients reviewed by two investigators, were superficial spongiform pustules (66%), papillary oedema (61%), polymorphous perivascular infiltrate with eosinophils (34%), and leukocytoclastic vasculitis with fibrinoid deposits (20%). Focal necrosis of keratinocytes was observed in 25% and the epidermis was normal or spongiotic without psoriasiform hyperplasia in 61%.

In comparison, the present study of 102 AGEP cases disclosed several unique histopathological features: 1) sub/intracorneal pustules and intraepidermal pustules, often contiguous with sub/intracorneal pustules; 2) the pustules showed a higher prevalence of spongiform features (95% of intraepidermal pustules); 3) a higher prevalence of necrotic keratinocytes (67%), papillary oedema (88%), and dermal eosinophils (81%); (4) a marked prevalence of interstitial and mid/deep-dermal infiltrates (93% and 95%, respectively) and of dermal neutrophils (100%), not emphasised previously; 5) psoriasiform hyperplasia (rete ridge elongation, clubbing, and fusion at rates of 76%, 51%, 81%, respectively) was usually mild, although more common than previously reported. Munro abscesses, which are generally associated with psoriasis, were observed in 17% of the cases; 6) on the other hand, vasculitis, which was strictly defined by the presence of vascular fibrinoid alteration and leucocytoclasia, was observed in the present study only once, indicating that vasculitis is not a diagnostic feature of AGEP. Since erythrocyte extravasation occurred in 54% of the cases, the previously reported high rate of vasculitis in AGEP might be attributed to misinterpretation of leukocytoclasia and/or erythrocyte extravasation as vasculitis, or to a diagnostic confusion of AGEP with pustular vasculitis.[34]; 7) histologically, follicular pustules were found in 23% of the cases. Although the distribution of the pustular eruption in AGEP is mostly non-follicular,[13] the occurrence of follicular pustules in association with non-follicular pustules has been reported.[3,5] Thus, the presence of follicular pustules would appear not to exclude the diagnosis of AGEP.

Differences between the histopathological features of AGEP reported in various case reports and clinical studies might be attributed to case definition or different stages in the evolution of the skin lesions analysed. It was shown in a study of 21 AGEP cases[26] that the histopathological features vary in relation to the age of the skin lesion. Thus, biopsies of early lesions showed marked to moderate papillary dermal oedema and a mixed dermal

inflammatory infiltrate, often with erythrocyte extravasation, and some leukocytoclasia. Biopsies of well-developed lesions showed spongiform pustules within the epidermis and occasional dyskeratotic cells with residual perivascular dermal oedema. Although no definitive vasculitis was seen, leukocytoclasia was observed within the dermal infiltrate in the majority of biopsy specimens obtained more than 48 hours after the onset of the eruption.

A wide spectrum of pustular reactions can easily be differentiated from AGEP both clinically and histologically (e.g. bacterial folliculitis, acne, dermatophyte infections, impetigo, infantile chronic acropustulosis, Sweet's syndrome, IgA pemphigus, necrolytic migratory erythema, bowel bypass syndrome, Behçet's disease, and staphylococcal scalded skin syndrome). However, the differential diagnosis between AGEP and generalised PP, especially the acute von Zumbusch type, may be difficult clinically and histologically.. Various histological features in PP bear similarity to AGEP, including superficial spongiform pustules, neutrophils beneath the stratum corneum, acanthosis, and papillary oedema. On the other hand, characteristic for PP is the spongiform macropustule, arising from neutrophils that migrate from the dermal papillary capillaries into the epidermis, while dermal infiltrates are superficial and lymphocytic, usually lacking eosinophils. In addition, classical epidermal changes of psoriasis vulgaris vary and may be rather prominent in PP.[35,36]

Several histopathological features that were observed in the present study, may point to the diagnosis of AGEP. These include superficial spongiform pustules, spongiosis, exocytosis of neutrophils, necrotic keratinocytes, papillary oedema, mixed dermal infiltrates, including mid/deep-dermal and interstitial infiltrates, containing neutrophils and eosinophils, and the paucity of classical plaque-type psoriatic changes (i.e., Munro abscesses, absence of granular layer, suprapapillary plate thinning, tortuous and dilated blood vessels). The diagnosis of AGEP may be based on these key histopathological features combined with clinical signs in favour of AGEP including an abrupt onset, a short duration (≤ 15 days), association with

recently introduced drugs, spontaneous resolution after withdrawal of the culprit drugs, and a non-recurrent tendency.[2,6,13]

It has been reported that AGEP may occur in patients with psoriasis.[2,13] Accordingly, AGEP has been alleged to be a variant of PP, that could be triggered by a variety of exogenous triggers such as drugs or infections.[13,22-25,37] In the present study a personal history of psoriasis was recorded in 16 (15.6%) of the 102 AGEP cases. No significant differences were observed between the sub-group of 16 AGEP cases with a personal history of psoriasis and the other 86 AGEP cases. Nevertheless, our study does not support the assumption that any acute pustular eruption, occurring in patients with a psoriatic background, is necessarily PP.

Several of the prevalent key features in favour of AGEP may imply its aetiopathogenesis:

a) The prominent presence of eosinophils in the skin of AGEP patients, both within the pustules and in the dermis, is in agreement with the presence of blood eosinophilia observed in about a third of AGEP patients.[13] The presence of tissue and blood eosinophilia, which is a hallmark of many drug-induced allergic reactions, suggests that AGEP is a hypersensitivity reaction, probably drug-induced.[38,39] Eosinophilia observed in AGEP may be attributed to the rare presence of IL8/CXCL8 producing T-cell clones, which display a Th2-type cytokine profile with high IL-4 and IL-5 secretion.[40-42]

b) The presence of necrotic keratinocytes in AGEP, has been reported in other drug eruptions including exanthematic drug eruptions and drug eruptions characterised primarily by interface dermatitis such as lichenoid drug eruptions, Stevens Johnson syndrome (SJS), toxic epidermal necrolysis (TEN), and fixed drug eruptions.[43] Although SJS or TEN are drug-induced reactions manifested by full thickness epidermal necrosis and only a very sparse inflammatory infiltrate, some similarity

may exist between AGEP and SJS or TEN.[27,44] The necrotic keratinocytes observed in AGEP can be induced by cytotoxic drug-specific T-cells (CD8+ or CD4+).[45]

c) The neutrophilic inflammation observed in AGEP is unusual in allergic drug reactions. The prominent presence of dermal neutrophils in AGEP may reflect their recruitment by the potent neutrophil-attracting chemokine IL-8/CXCL8, secreted by drug-specific T-cells (CD4+ and CD8+) and keratinocytes. Factors produced by the IL8/CXCL8-producing T-cells reduce neutrophil apoptosis, thus enhancing neutrophil survival and leading to the sterile pustular eruption found in AGEP.[39-42]

d) The mid/deep-dermal perivascular infiltrates and extravasation of erythrocytes, which were observed in AGEP have been reported in other drug-induced eruptions, even in the absence of vasculitis, and may point to a drug etiology.[38,46]

In conclusion, the present study, conducted in a large series of AGEP patients with a validated diagnosis, disclosed a spectrum of histopathological features that provides additional support for the concept that AGEP is a separate entity that can occur as an acute episode, even in patients with psoriasis.

REFERENCES

1 Beylot C, Bioulac P, Doutre MS. [Acute generalized exanthematic pustuloses (four cases) (author's transl)]. *Ann Dermatol Venereol* 1980; **107**: 37-48.

2 Sidoroff A, Dunant A, Viboud C *et al.* Risk factors for acute generalized exanthematous pustulosis (AGEP)-results of a multinational case-control study (EuroSCAR). *Br J Dermatol* 2007; **157**: 989-996.

3 Davidovici BB, Pavel D, Cagnano E *et al.* Acute generalized exanthematous pustulosis following a spider bite: report of 3 cases. *J Am Acad Dermatol* 2006; **55**: 525-529.

4 Davidovici BB, Naveh HP, Cagnano E *et al.* [Acute generalized exanthematous pustulosis (AGEP) following intake of furosemide]. *Harefuah* 2006; **145**: 477-479.

5 Davidovici B, Dodiuk-Gad R, Rozenman D *et al.* Profile of acute generalized exanthematous pustulosis in Israel during 2002-2005: results of the RegiSCAR Study. *Isr Med Assoc J* 2008; **10**: 410-412.

6 Halevy S. Acute generalized exanthematous pustulosis. *Curr Opin Allergy Clin Immunol* 2009; **9**: 322-8.

7 Rouchouse B, Bonnefoy M, Pallot B *et al.* Acute generalized exanthematous pustular dermatitis and viral infection. *Dermatologica* 1986; **173**: 180-184.

8 Naides SJ, Piette W, Veach LA *et al.* Human parvovirus B19-induced vesiculopustular skin eruption. *Am J Med* 1988; **84**: 968-972.

9 Haro-Gabaldon V, Sanchez-Sanchez-Vizcaino J, Ruiz-Avila P *et al.* Acute generalized exanthematous pustulosis with cytomegalovirus infection. *Int J Dermatol* 1996; **35**: 735-737.

10 Feio AB, Apetato M, Costa MM *et al.* [Acute generalized exanthematous pustulosis due to Coxsackie B4 virus]. *Acta Med Port* 1997; **10**: 487-491.

11 Lerch M, Bircher AJ. Systemically induced allergic exanthem from mercury. *Contact Dermatitis* 2004; **50**: 349-353.

12 Belhadjali H, Mandhouj S, Moussa A *et al.* Mercury-induced acute generalized exanthematous pustulosis misdiagnosed as a drug-related case. *Contact Dermatitis* 2008; **59**: 52-54.

13 Roujeau JC, Bioulac-Sage P, Bourseau C *et al.* Acute generalized exanthematous pustulosis. Analysis of 63 cases. *Arch Dermatol* 1991; **127**: 1333-1338.

14 Roujeau JC. Clinical heterogeneity of drug hypersensitivity. *Toxicology* 2005; **209**: 123-129.

15 Staughton RC, Payne CM, Harper JI *et al.* Toxic pustuloderma--a new entity? *J Royal Soc Med* 1984; **77** Suppl 4: 6-8.

16 Rustin MH, Robinson TW, Dowd PM. Toxic pustuloderma: a self-limiting eruption. *Br J Dermatol* 1990; **123**: 119-24.

17 Bissonnette R, Tousignant J, Allaire G. Drug-induced toxic pustuloderma. *Int J Dermatol* 1992; **31**: 172-174.

18 Macmillan AL. Generalised pustular drug rash. *Dermatologica* 1973; **146**: 285-91.

19 Shelley ED, Shelley WB. The subcorneal pustular drug eruption: an example induced by norfloxacin. *Cutis* 1988; **42**: 24-7.

20 Lotem M, Ingber A, Segal R *et al.* Generalized pustular drug rash induced by hydroxychloroquine. *Acta Derm Venereol* 1990; **70**: 250-1.

21 Lazarov A, Livni E, Halevy S. Generalized pustular drug eruptions: confirmation by in vitro tests. *J Eur Acad Dermatol Venereol* 1998; **10**: 36-41.

22 Baker H, Ryan TJ. Generalized pustular psoriasis. A clinical and epidemiological study of 104 cases. *Br J Dermatol* 1968; **80**: 771-793.

23 Whittam LR, Wakelin SH, Barker JN. Generalized pustular psoriasis or drug-induced toxic pustuloderma? The use of patch testing. *Clin Exp Dermatol* 2000; **25**: 122-4.

24 Burrows NP, Russell Jones RR. Pustular drug eruptions: a histopathological spectrum. *Histopathology* 1993; **22**: 569-573.

25 Spencer JM, Silvers DN, Grossman ME. Pustular eruption after drug exposure: is it pustular psoriasis or a pustular drug eruption? *Br J Dermatol* 1994; **130**: 514-519.

26 Smith K, Norwood C, Skelton H. Do the physical and histologic features and time course in acute generalized exanthematous pustulosis reflect a pattern of cytokine dysregulation? *J Cutan Med Surg* 2003; **7**: 7-12.

27 Cohen AD, Cagnano E, Halevy S. Acute generalized exanthematous pustulosis mimicking toxic epidermal necrolysis. *Int J Dermatol* 2001; **40**: 458-461.

28 Kardaun SH, de Monchy JG. Acute generalized exanthematous pustulosis caused by morphine, confirmed by positive patch test and lymphocyte transformation test. *J Am Acad Dermatol* 2006; **55**: S21-3.

29 Paradisi A, Bugatti L, Sisto T *et al.* Acute generalized exanthematous pustulosis induced by hydroxychloroquine: three cases and a review of the literature. *Clin Ther* 2008; **30**: 930-940.

30 Mockenhaupt M, Viboud C, Dunant A *et al.* Stevens-Johnson syndrome and toxic epidermal necrolysis: Assessment of medication risks with emphasis on recently marketed drugs. The EuroSCAR-study. *J Invest Dermatol* 2007: (in press).

31 Kardaun SH, Sidoroff A, Valeyrie-Allanore L *et al.* Variability in the clinical pattern of cutaneous side-effects of drugs with systemic symptoms: does a DRESS syndrome really exist? *Br J Dermatol* 2007; **156**: 609-11.

32 Valeyrie-Allanore L, Poulalhon N, Fagot JP *et al.* Stevens-Johnson syndrome and toxic epidermal necrolysis induced by amifostine during head and neck radiotherapy. *Radiother Oncol* 2008; **87**: 300-3.

33 Sidoroff A, Halevy S, Bavinck JN *et al.* Acute generalized exanthematous pustulosis (AGEP)--a clinical reaction pattern. *J Cutan Pathol* 2001; **28**: 113-119.

34 Rockl H. [Leukocytoclastic vasculitis due to drug allergy presenting as generalized pustular exanthema]. *Hautarzt* 1981; **32**: 467-70.

35 Mobini N, Toussaint S, Kamino H. Noninfectious erythemathous, papular, and squamous diseases. In: Lever's Histology of the Skin (Elder DE, ed), 9th edn. Philadelphia, PA: Lippincott Williams & Wilkins. 2005.

36. Ackerman AB, Böer A, Bennin B, Gottlieb GJ. Histologic diagnosis of inflammatory skin diseases. 3rd ed. New York:Ardor Scribendi;2005.

37 Beylot C, Doutre MS, Beylot-Barry M. Acute generalized exanthematous pustulosis. *Semin Cutan Med Surg* 1996; **15**: 244-249.

38 Ramdial PK, Naidoo DK. Drug-induced cutaneous pathology. *J Clin Pathol* 2009; **62**: 493-504.

39 Pichler WJ, Yawalkar N, Britschgi M *et al.* Cellular and molecular pathophysiology of cutaneous drug reactions. *Am J Clin Dermatol* 2002; **3**: 229-238.

40 Britschgi M, Pichler WJ. Acute generalized exanthematous pustulosis, a clue to neutrophil-mediated inflammatory processes orchestrated by T cells. *Curr Opin Allergy Clin Immunol* 2002; **2:** 325-331.

41 Britschgi M, Steiner UC, Schmid S *et al.* T-cell involvement in drug-induced acute generalized exanthematous pustulosis. *J Clin Invest* 2001; **107**: 1433-1441.

42 Schaerli P, Britschgi M, Keller M *et al.* Characterization of human T cells that regulate neutrophilic skin inflammation. *J Immunol* 2004; **173**: 2151-2158.

43 Horn TD, Hiatt KM. Cutaneous toxicities of drugs. In: Lever's Histology of the Skin (Elder DE, ed), 9th edn. Philadelphia, PA: Lippincott Williams & Wilkins. 2005.

44 Meiss F, Helmbold P, Meykadeh N *et al.* Overlap of acute generalized exanthematous pustulosis and toxic epidermal necrolysis: response to antitumour necrosis factor-alpha antibody infliximab: report of three cases. *J Eur Acad Dermatol Venereol* 2007; **21**: 717-719.

45 Schmid S, Kuechler PC, Britschgi M *et al.* Acute generalized exanthematous pustulosis: role of cytotoxic T cells in pustule formation. *Am J Pathol* 2002; **161**: 2079-86.

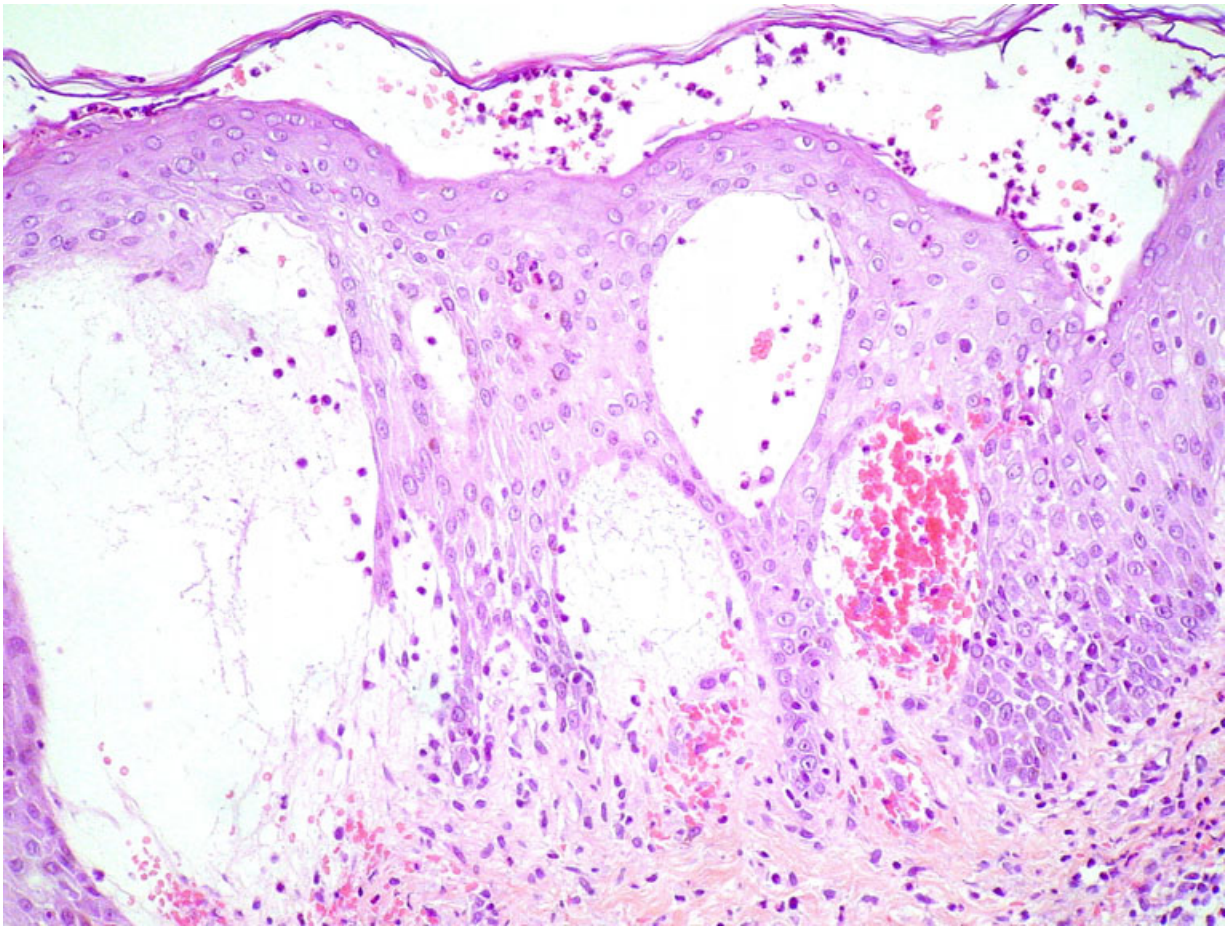
46 Pang BK, Su D, Ratnam KV. Drug-induced purpura simplex: clinical and histological characteristics. *Ann Acad Med* Singapore 1993; **22**: 870-2.

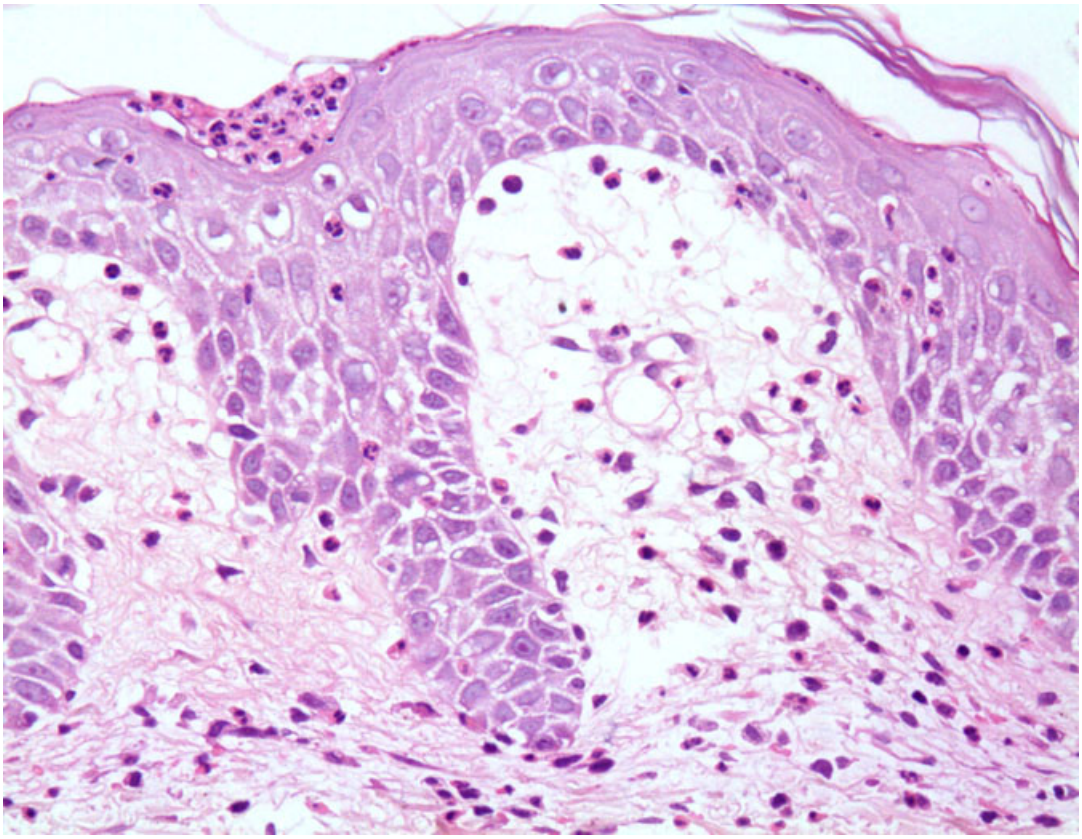
LEGENDS TO FIGURES

Figure 1. Large non-spongiform subcorneal pustule, papillary oedema, and erythrocyte extravasation (haematoxylin-eosin stain, original magnification x 200).

Figure 2. Small subcorneal pustule, presence of neutrophils and eosinophils in the epidermis and in the superficial dermis (haematoxylin-eosin stain, original magnification x 400).

Figure 3. Large spongiform intraepidermal pustule with necrotic keratinocytes and spongiosis in the lower part of the epidermis. In the dermis there is discrete leucocytoclasia, but no vasculitis (haematoxylin-eosin stain, original magnification x 200).





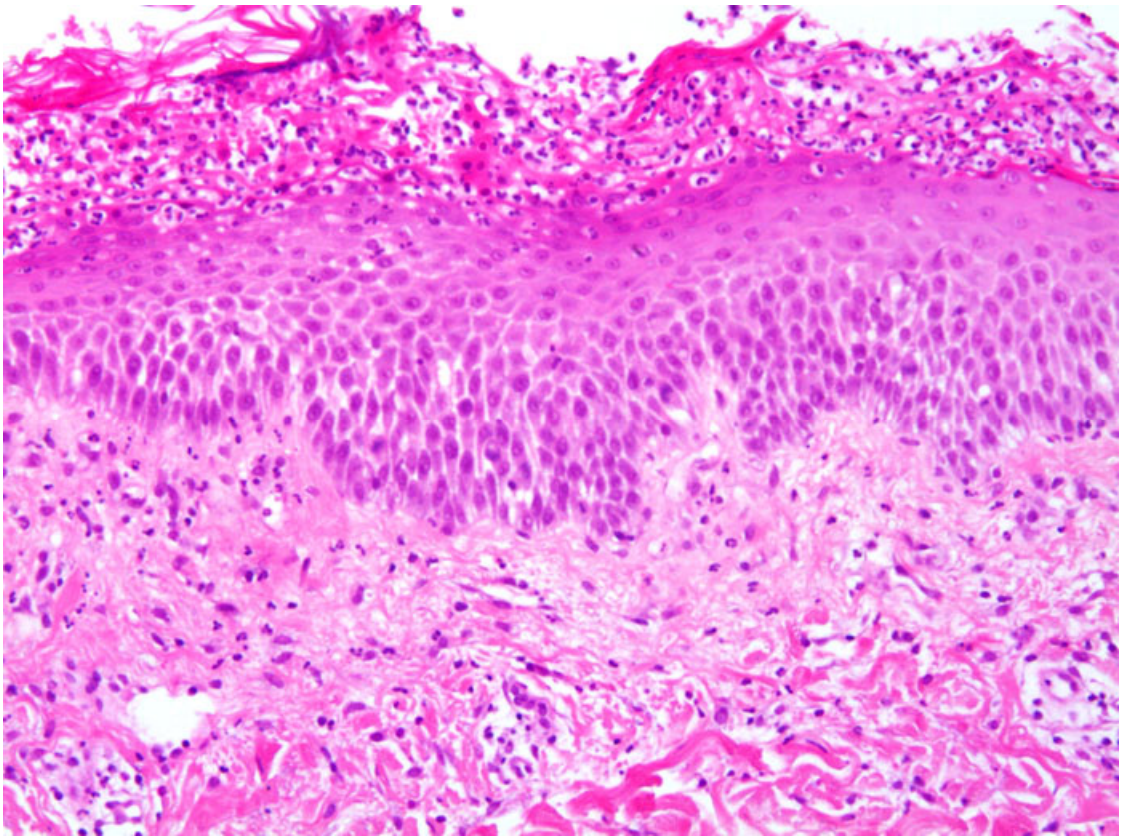


Table 1: Histopathological parameters used in the evaluation of AGEP

Histological parameter	Degree of severity	Histological parameter	Degree of severity
Pustule size*		**Eosinophils** (pustule or dermis)**/erythrocyte extravasation**	
small (<10 keratinocytes)	1	1 or 2 cells	1
medium (10–15 keratinocytes)	2	>2	2
large (> 15 keratinocytes)	3	many	3
Spongiform pustule†		**Munro abscess**	
mild	1	1	1
moderate	2	2	2
prominent	3	>2	3
Follicular pustule		**Hyperkeratosis**	
accessory‡	1	mild	1
predominant	2	moderate	2
solitary§	3	prominent	3
Spongiosis		**Granular cell layer/parakeratosis††**	
		absent	0
mild	1	up to 1/3 the length of the biopsy	1
prominent	2	up to 2/3 the length of the biopsy	2
vesicles	3	almost total	3
Exocytosis of neutrophils		**Suprapapillary plate thinning‡‡**	
a few	1	1 papilla	1
scattered	2	2 papillae	2
many	3	>2 papillae	3
Necrotic keratinocytes		**Tortuous and dilated blood vessels/vasculitis§§**	
1 or 2	1	1 vessel	1
>2	2	2 vessels	2
segmental necrosis or more	3	>2 vessels	3
Papillary oedema		**Rete ridges elongation/clubbing/fusion**	
discrete	1	1	1
moderate	2	2	2
severe	3	>2	3
Infiltrates: superficial, interstitial, mid/deep-dermal		**Mitosis**	
discrete	1	number per high power field	
moderate	2	(x40 magnification)	
dense	3		
Dermal neutrophils			
a few	1		
scattered	2		
full fields	3		

***** In case of several pustules, the largest is used.
† Accumulation of micro-aggregates of neutrophils separated by degenerated and thinned keratinocytes.
‡ In conjunction with other types of pustules only.
§ Without other types of pustules.
†† Parakeratosis/granular layer above a pustule is not included.
‡‡ Suprapapillary plate thinning of the epidermis is defined as less than 3 layers of keratinocytes above the papillae.
§§ Leucocytoclastic vasculitis.

Table 2: The prevalence of histopathological parameters in 102 AGEP patients

Histopathological parameter	Degree of severity	Prevalence (%)
Pustules		
Sub/intracorneal and intraepidermal pustules		**94 (92)**
Sub/intracorneal pustules		**39 (41)**
large	3	32 (82)
small	1	4 (10)
spongiform	1,2,3	17 (44)
presence of eosinophils	1,2,3	14 (36)
Intraepidermal pustules		**19 (20)**
large	3	17 (89)
small	1	2 (10)
spongiform	1,2,3	18 (95)
presence of eosinophils	1,2,3	6 (32)
Combined (sub/intracorneal and intraepidermal)		**36 (38)**
Follicular pustules		**22 (23)**
accessory (in conjunction with other pustules)	1	8 (36)
predominant	2	9 (41)
solitary	3	5 (23)
Epidermis		
Spongiosis		**82 (80)**
mild	1	62 (76)
Exocytosis of neutrophils		**79 (77)**
A few	1	53 (67)
Necrotic keratinocytes		**68 (67)**
1-2 keratinocytes	1	32 (47)
>2 keratinocytes	2	31 (46)
segmental necrosis	3	5 (7)
Dermis		
Papillary oedema		**90 (88)**
discrete	1	41 (45)
moderate	2	24 (27)
severe	3	25 (28)
Superficial infiltrates		**102 (100)**
moderate	2	76 (74)
Mid/deep-dermal infiltrates		**97 (95)**
discrete	1	64 (66)
Interstitial infiltrates		**95 (93)**
discrete	1	38 (40)
moderate	2	36 (38)
Dermal neutrophils		**102 (100)**
a few	1	24 (23)
scattered	2	60 (59)
Dermal eosinophils		**83 (81)**
a few	1	61 (73)
Vasculitis		**1 (1)**
Erythrocyte extravasation		**55 (54)**
1-2 cells	1	27 (49)
>2 cells	2	26 (47)
many	3	2 (4)

Histopathological parameter	Degree of severity	Prevalence (%)
Classical plaque-type psoriatic changes		
Munro abscess		**17 (17)**
1	1	10 (59)
≥2	2,3	7 (41)
Granular cell layer		**99 (97)**
none	0	3 (3)
Parakeratosis		**63 (62)**
mild	1	35 (55)
moderate	2	24 (38)
Hyperkeratosis		**26 (25)**
mild	1	25 (96)
Suprapapillary plate thinning		**7 (7)**
mild	1	7 (100)
Tortuous and dilated blood vessels		**16 (16)**
mild	1	8 (50)
moderate	2	8 (50)
Rete ridge elongation		**78 (76)**
mild	1	38 (49)
moderate	2	32 (41)
Rete ridge clubbing		**52 (51)**
mild	1	39 (75)
Rete ridge fusion		**83 (81)**
mild	1	35 (42)
moderate	2	39 (47)
Mitosis		
number per high-power field (x40 magnification)	mean	0.95