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# The histopathological spectrum of acute generalized exanthematous pustulosis (AGEP) and its differentiation from generalized pustular psoriasis

**Background:** Acute generalized exanthematous pustulosis (AGEP) represents a severe, acute, pustular skin reaction that is most often induced by drugs. AGEP can be difficult to differentiate from generalized pustular psoriasis (GPP) both clinically and histopathologically. We present a systematic description of the histopathological spectrum of AGEP and GPP with a focus on discriminating features.

**Materials and methods:** A retrospective, descriptive, comparative histopathological study was completed utilizing step sections of 43 biopsies of 29 cases with a validated diagnosis of probable or definite AGEP and 24 biopsies of 19 cases with an established diagnosis of GPP.

**Results:** In AGEP, biopsies from erythema and pustules showed minor differences, whereas histopathology of the acute stage of GPP showed major differences compared to the chronic stage. Comparing AGEP and GPP, the presence of eosinophils, necrotic keratinocytes, a mixed interstitial and mid-dermal perivascular infiltrate and absence of tortuous or dilated blood vessels were in favor of AGEP. Moreover, chronic GPP was characterized by prominent epidermal psoriatic changes. The frequency of a psoriatic background of AGEP patients in our study was higher than that of psoriasis in the general population. However, histopathology of a subgroup of AGEP patients with a personal history of psoriasis revealed no significant differences from the other AGEP patients.

**Conclusions:** The spectrum of histopathological features of both AGEP and GPP is presented. Despite considerable overlap, subtle consistent histopathological differences and the grade of severity of specific features can help in differentiation. We could neither substantiate earlier reports that follicular pustules exclude AGEP nor did we see vasculitis as a specific feature in AGEP. Our study also supports the concept that AGEP is a separate entity that is distinct from GPP.

Kardaun SH, Kuiper H, Fidler V, Jonkman MF. The histopathological spectrum of acute generalized exanthematous pustulosis (AGEP) and its differentiation from generalized pustular psoriasis.

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In the past, most widespread sterile pustular eruptions were classified as generalized pustular psoriasis (GPP), a rare variant of psoriasis with several subtypes. The most severe and recalcitrant variant, the von Zumbusch type, is characterized by an acute generalized eruption of pustules on an erythematous base, sometimes lasting for weeks and often accompanied by fever and leukocytosis. Other types, such as annular pustular psoriasis, are subacute or even chronic and can either be widespread or localized. Psoriasis vulgaris may proceed, accompany or follow the pustular episode.<sup>1–3</sup>

In 1968, in a comprehensive review of 104 cases of GPP, Baker and Ryan<sup>1</sup> identified on clinical grounds five cases of exanthematous pustular psoriasis with short self-limiting courses which were presumably precipitated by infections and/or drugs. In 1980, Beylot et al.<sup>4</sup> termed this rare reaction type as acute generalized exanthematous pustulosis (AGEP). AGEP is mainly induced by drugs, but occasionally it can be precipitated by other causes such as viral infections.<sup>5</sup> Pustular rashes similar to AGEP have been described as toxic pustuloderma, pustular drug rash, (subcorneal) pustular drug eruption or drug-induced GPP.<sup>6–10</sup>

Clinically, AGEP is characterized by the sudden appearance of dozens of sterile, non-follicular, small pustules on edematous erythema with a widespread distribution or a predilection for the face and/or skin folds. Mild non-erosive mucosal involvement, mostly oral, may sometimes occur. Other skin signs such as facial edema, purpura, target-like lesions and blisters have been described but are not typical for AGEP. Fever, neutrophilia and peripheral blood eosinophilia (in a third of patients) are present. After elimination of the causative culprit, pustules associated with AGEP disappear in a few days, typically followed by postpustular desquamation, and the reaction fully resolves within 15 days. Usually, internal organs are not involved and overall prognosis is good, although lethal outcome has been reported.<sup>11,12</sup>

AGEP can be difficult to differentiate from GPP both clinically and histopathologically. Clinically, signs in favor of AGEP are abrupt onset, short duration, polymorphous lesions, association with recently started drugs and spontaneous healing after their elimination, non-recurrence and absence of arthritis or a personal or family history of psoriasis. Knowledge of the histopathology of both AGEP and GPP is based on case reports and small clinical studies.<sup>4,13–22</sup> Histopathological differentiation of AGEP from GPP has not been well documented and some even consider distinction based strictly on dermatopathology to be impossible.<sup>23</sup> The aim of the present study was to characterize the

histopathological spectrum of AGEP and GPP and to find clues for differentiating these two disorders.

### Materials and methods

#### Materials

We included 29 consecutive cases, evaluated as definite or probable AGEP, and 19 consecutive cases of GPP, that visited the Department of Dermatology of the University Medical Center Groningen between 1992 up until mid-2009 and for which biopsies of the active phase were available. All patients were seen in the active phase of the disease. Clinical information, charts, photographs, slides and information on the type and duration of the lesion from which the biopsy was taken were available. Diagnosis and grade of probability of AGEP (23 definite and 6 probable) were evaluated according to the validation system of Sidoroff et al.<sup>11</sup> Diagnosis of GPP was based on history, course, clinical charts and photographs.<sup>1–3</sup>

Biopsies were divided into subgroups: those for AGEP taken from erythema or a visible pustule, and those for GPP taken from acute pustules on erythematous, recently uninvolved skin representing acute GPP (aGPP), or from pustules on longer existing lesions, representing chronic GPP (cGPP). In each subgroup, only one biopsy of a case was randomly selected.

From the enrolled cases of AGEP, 43 biopsies (27 from visible pustules and 16 from erythema) and from GPP, 24 biopsies (14 from aGPP and 10 from cGPP) were studied.

#### Pathologic evaluation

The study was performed on step sections (regularly including additional step sections) of paraffin-embedded tissue, stained with hematoxylin and eosin. All processed slides were systematically evaluated according to parameters and grades listed in Table 1. Scoring was based on independent investigation by the first two authors, followed by a mutual meeting at a two-headed microscope where consensus was reached. The first author was the treating physician, not blinded for diagnosis, while the second author had no other information than the pending differential diagnosis.

#### Statistical analysis

We used the Fisher exact test for comparison of groups with respect to dichotomous variables. For comparison of groups with respect to severity scores, a linear trend test with exact calculated p values was used. A two-sided p value of 0.05 or less was considered as statistically significant. Data were analyzed using SPSS (version 16, SPSS, Chicago, IL).

Table 1. Scoring system of histopathological parameters used for evaluation of acute generalized exanthematous pustulosis and generalized pustular psoriasis

Parameter/severity score	0	1	2	3
Pustule size*	No	<10 Keratinocytes	10–15 Keratinocytes	16–30 Keratinocytes
Macro-pustule size	No	31–60 Keratinocytes	>60 Keratinocytes	—
Spongiform character pustule	No	Mild	Moderate	Severe
Munro(-like) abscesses	No	1	2	>2
Hair follicular pustule	No	Accessory <sup>†</sup>	Predominant	Solitary <sup>‡</sup>
Necrotic keratinocytes	No	1 or 2	3–10	>10
Neutrophilic exocytosis	No	Few	Scattered	Many
Spongiosis	No	Mild	Moderate	Vesicles
Papillary edema	No	Mild	Moderate	Severe
Infiltrates	No	Mild	Moderate	Dense
Eosinophils (pustule)	No	1 or 2	3–5	>5
Eosinophils (dermal)	No	1 or 2	3–10	>10
Neutrophils (dermal, papillary)	No	Few	Scattered	Full fields
Leukocytoclasia	No	Mild	Moderate	Severe
Vasculitis	No	1 Vessel	2 Vessels	>2 Vessels
Hyperkeratosis	No	Mild	Moderate	Severe
Parakeratosis	No	Mild	Moderate	Severe
Granular cell layer	Totally preserved	Mostly preserved	Severely diminished	Missing
Rete ridge changes (elongation, fusion and/or clubbing)	No	Mild	Moderate	Severe
Mitosis	No	<1.5/HPF	1.5–2.4/HPF	≥2.5/HPF
Suprapapillary plate thinning	No	1 Papilla	2 Papillae	>2 Papillae
Tortuous, dilated blood vessels	No	1 Capillary loop	2 Capillary loops	>2 Capillary loops

HPF, high power field at magnification 40× (0.25 mm<sup>2</sup>).

\*Pustule size: in case of several pustules, the largest is documented.

<sup>†</sup>Only in conjunction with other types of pustules (hair follicular pustule, accessory).

<sup>‡</sup>Without other types of pustules (hair follicular pustule, solitary).

## Results

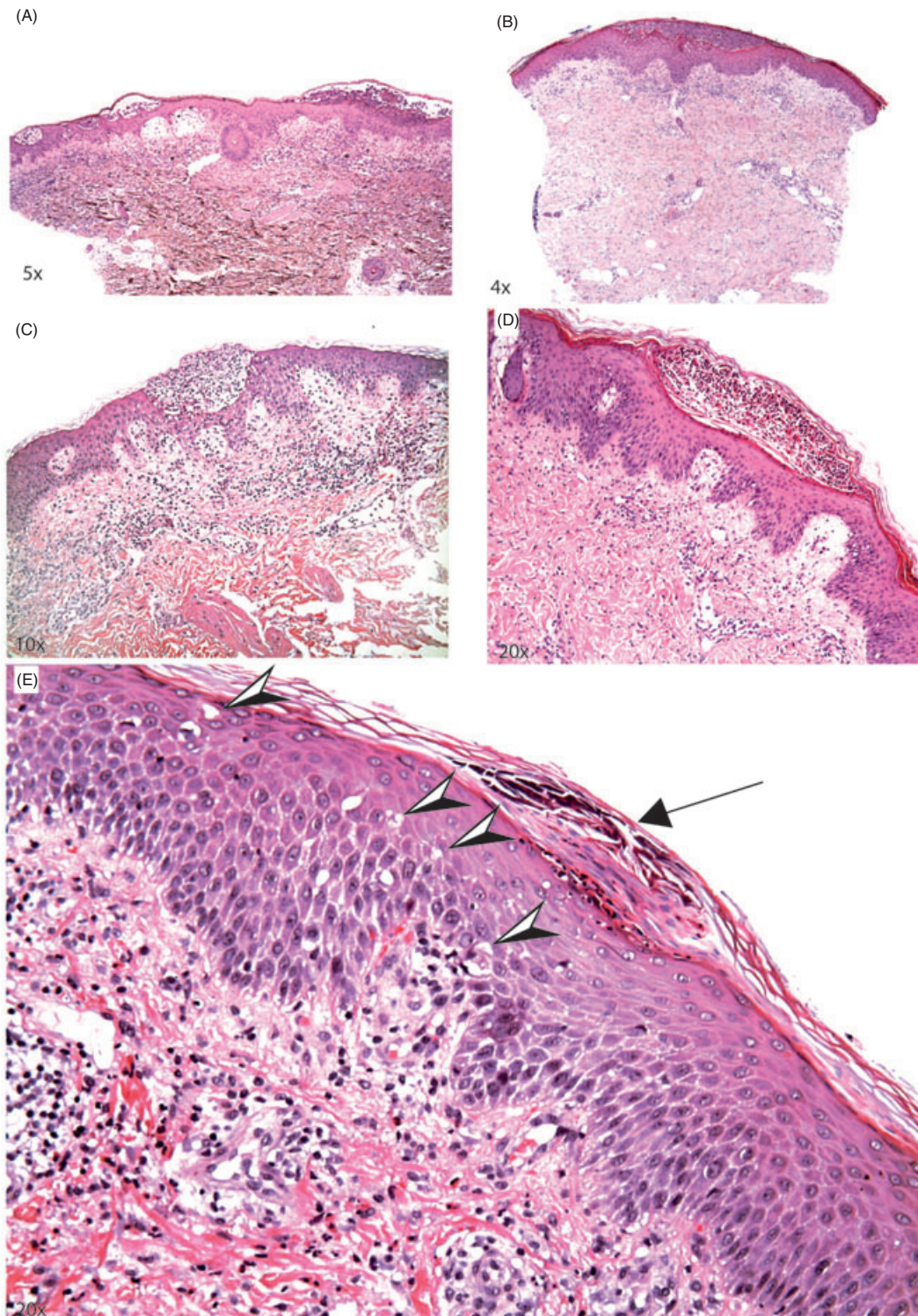
The gender–age distribution in AGEp was 12 male, 17 female, mean age 58.2 years (range 3–86), and in GPP 5 male, 14 female, mean age 55.6 years (range 0–80).

The detailed spectrum of the histopathological features in our study of 43 biopsies (27 from pustules and 16 from erythema) of AGEp is presented in Table 2. All biopsies showed at least one pustule. We observed intracorneal and subcorneal pustules, sometimes contiguous to intraepidermal or intracorneal, and combinations of these pustules in various sizes (Fig. 1A,E). Although often present at several levels, the accent of the pustules was generally subcorneal to subcorneal/intraepidermal. All pustules were neutrophil-rich with acantholytic epidermal cells and 58% also contained eosinophils (generally sparse). Most spongiform were the subcorneal/intraepidermal pustules (Fig. 1C). Although pustules were generally non-follicular, follicular pustules were observed as well (26%), most often accessory to other pustules, but incidentally also solitary. Munro(-like) abscesses (Fig. 1E) were noticed in 21% and macro-pustules in 40% of the biopsies (Fig. 1A,B,D).

Solitary necrotic keratinocytes (88%), most often discrete, neutrophilic exocytosis (91%) and spongiosis (100%) were common (Fig. 1C,E). Papillary edema (91%) was mostly discrete (Fig. 1A,C,D). Superficial and mid-dermal perivascular infiltrates, as well as interstitial infiltrates, were always present and of a mixed cellular type, generally also containing neutrophils (100%) and eosinophils (95%) (Fig. 1A–E). Often, mid-dermal infiltrates were also localized rather deep, lower than the upper third of the mid-dermis. The majority of cases showed erythrocyte extravasation and leukocytoclasia (Fig. 1E), but vasculitis, expressed by fibrinoid changes of the endothelial wall, was seen in only one patient.

Parakeratosis and rete ridge changes such as elongation, clubbing and fusion were regularly present, but often rather discrete. Other psoriasiform features such as hyperkeratosis, suprapapillary plate thinning and tortuous, dilated blood vessels were absent or only seen in a minority (Fig. 1D). The mitotic rate was generally under 1.5/high power field of 0.25 mm<sup>2</sup>.

Histopathologically biopsies taken from erythema all revealed small pustules, mainly subcorneal to subcorneal/intraepidermal, whereas those from visible pustules were generally large with a more



*Fig. 1.* Histopathology of acute generalized exanthematous pustulosis. A) Spongiform pustules at various epidermal levels. B) Slightly spongiform subcorneal macro-pustule with a superficial and (lower) mid-dermal, perivascular and interstitial dermal infiltrate. C) Slightly spongiform subcorneal-intraepidermal pustule, minor acanthotic rete ridge changes, spongiosis, neutrophilic exocytosis, papillary edema and a mixed perivascular and interstitial infiltrate. D) Subcorneal macro-pustule, slightly acanthotic rete ridge changes, papillary edema, dilated papillary vessels, mixed perivascular and interstitial infiltrates. E) Small sub-/intraepidermal pustule contiguous with a Munro-like abscess (arrow), spongiosis, few epidermal necrotic keratinocytes (arrowheads), erythrocyte extravasation, discrete leukocytoclasia and mixed perivascular and interstitial infiltrate including eosinophils. Hematoxylin and eosin, original magnification: (A)  $\times 50$ , (B)  $\times 40$ , (C)  $\times 100$  and (D,E)  $\times 200$ .

Table 2. Prevalence of histopathological features in pustules and erythema in AGEP

Histopathological parameters	Prevalence		
	AGEP total <i>n</i> = 43 (grade 2,3)	AGEP pustule <i>n</i> = 27 (grade 2,3)	AGEP erythema <i>n</i> = 16 (grade 2,3)
<b>Pustules</b>			
Munro(-like) abscesses	9 (5)	7 (4)	2 (1)
Intra-/subcorneal pustules	39 (24)	24 (18)	15 (6)
<i>Spongiform</i>	31 (16)	18 (12)	13 (4)
Subcorneal-intraepidermal pustules	26 (24)	18 (18)	8 (6)
<i>Spongiform</i>	26 (18)	18 (15)	8 (3)
Eosinophils in pustule	25 (10)	16 (9)	9 (1)
Macro-pustules	17 (12)	17 (12)	0 (0)
Hair follicular pustules	11	8	3
<b>Epidermis</b>			
Necrotic keratinocytes	38 (23)	22 (16)	16 (7)
Neutrophilic exocytosis	39 (20)	26 (16)	13 (4)
Spongiosis	43 (19)	27 (12)	16 (7)
<b>Dermis</b>			
Papillary edema	39 (17)	25 (12)	14 (5)
Superficial infiltrate	43 (37)	27 (25)	16 (12)
Interstitial infiltrate	43 (21)	27 (17)	16 (4)
Upper mid-dermal infiltrate	43 (33)	27 (23)	16 (10)
Lower mid-dermal infiltrate	30 (8)	18 (5)	12 (3)
Eosinophils	41 (32)	26 (21)	15 (11)
Neutrophils infiltrate	43 (32)	27 (22)	16 (10)
Neutrophils papillary	38 (14)	26 (13)	12 (1)
Leukocytoclasia	33 (11)	24 (7)	9 (4)
<b>Psoriasiform (epidermal) changes</b>			
Hyperkeratosis	7 (0)	5 (0)	2 (0)
Parakeratosis	16 (3)	12 (3)	4 (0)
Stratum granulosum	9 (1)	8 (1)	1 (0)
Rete ridge changes	20 (11)	16 (11)	4 (0)
Mitosis	43 (6)	27 (4)	16 (2)
Suprapapillary plate thinning	0 (0)	0 (0)	0 (0)
Tortuous, dilated blood vessels	7 (1)	6 (1)	1 (0)

AGEP, acute generalized exanthematous pustulosis.

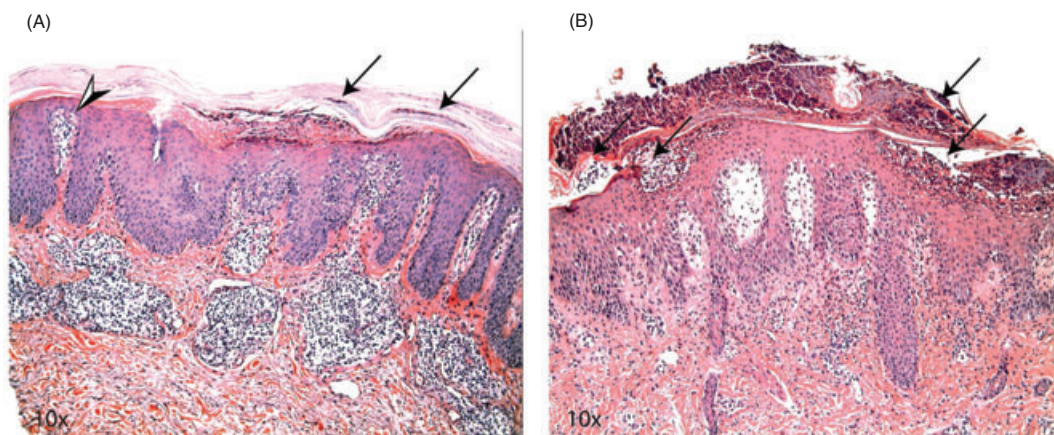


Fig. 2. Histopathology of chronic generalized pustular psoriasis (cGPP). A) Club-shaped psoriatic rete ridges with hyperkeratosis, parakeratosis, Munro abscesses (arrows), epidermal plate thinning and sub-/intracorneal pustule with dilated, tortuous vessels (arrowhead) and superficial perivascular mononuclear infiltrates. B) Hyperkeratosis, parakeratosis and psoriatic rete ridge elongation with pustules at several levels (arrows), neutrophilic exocytosis, mainly mononuclear perivascular infiltrate, and dilated papillary vessels. Hematoxylin and eosin, original magnification: (A,B)  $\times 100$ .

Table 3. Comparison of histopathological features in pustular lesion in AGEP, aGPP and cGPP

Histopathological parameters	Prevalence			Significance (p value)	
	AGEP pustule <i>n</i> = 27 (grade 2,3)	aGPP <i>n</i> = 14 (grade 2,3)	cGPP <i>n</i> = 10 (grade 2,3)	AGEP aGPP	AGEP cGPP
<b>Pustules</b>					
Munro(-like) abscesses	7 (4)	1 (1)	8 (8)	NS	<0.01
Intra-/subcorneal pustules	24 (18)	14 (14)	10 (10)	<0.01	0.02
<i>Spongiform</i>	18 (12)	14 (13)	10 (5)	<0.01	NS
Subcorneal-intraepidermal pustules	18 (18)	8 (8)	3 (3)	NS	0.02
<i>Spongiform</i>	18 (15)	8 (8)	3 (3)	NS	NS
Eosinophils in pustule	16 (9)	0 (0)	0 (0)	<0.01	<0.01
Macro-pustules	17 (12)	14 (13)	10 (4)	<0.01	0.01
Hair follicular pustules	8	3	2	NS	NS
<b>Epidermis</b>					
Necrotic keratinocytes	22 (16)	2 (0)	1 (0)	<0.01	<0.01
Neutrophilic exocytosis	26 (16)	13 (11)	10 (6)	NS	NS
Spongiosis	27 (12)	14 (5)	9 (0)	NS	<0.01
<b>Dermis</b>					
Papillary edema	25 (12)	13 (4)	7 (1)	NS	NS
Superficial infiltrate	27 (25)	14 (7)	10 (4)	<0.01	<0.01
Interstitial infiltrate	27 (17)	9 (3)	3 (1)	<0.01	<0.01
Upper mid-dermal infiltrate	27 (23)	5 (0)	7 (2)	<0.01	<0.01
Lower mid-dermal infiltrate	18 (5)	3 (0)	0 (0)	0.01	<0.01
Eosinophils	26 (21)	1 (0)	2 (0)	<0.01	<0.01
Neutrophils infiltrate	27 (22)	14 (6)	8 (4)	0.04	0.02
Neutrophils papillary	26 (13)	14 (13)	8 (5)	<0.01	NS
Leukocytoclasia	24 (7)	7 (2)	2 (0)	0.03	<0.01
<b>Psoriasiform (epidermal) changes</b>					
Hyperkeratosis	5 (0)	4 (2)	10 (8)	NS	<0.01
Parakeratosis	12 (3)	4 (2)	9 (6)	NS	<0.01
Stratum granulosum	8 (1)	10 (3)	10 (7)	0.03	<0.01
Rete ridge changes	16 (11)	6 (4)	10 (9)	NS	0.02
Mitosis	27 (4)	14 (5)	10 (7)	0.05	<0.01
Suprapapillary plate thinning	0 (0)	1 (0)	5 (2)	NS	<0.01
Tortuous, dilated blood vessels	6 (1)	13 (12)	10 (10)	<0.01	<0.01

AGEP, acute generalized exanthematous pustulosis; aGPP, acute generalized pustular psoriasis; cGPP, chronic generalized pustular psoriasis; NS, non-significant.

varied localization (Fig. 1A–D). Moreover, biopsies from pustules showed more pronounced rete ridge changes (Fig. 1C,D) and heavier infiltrates.

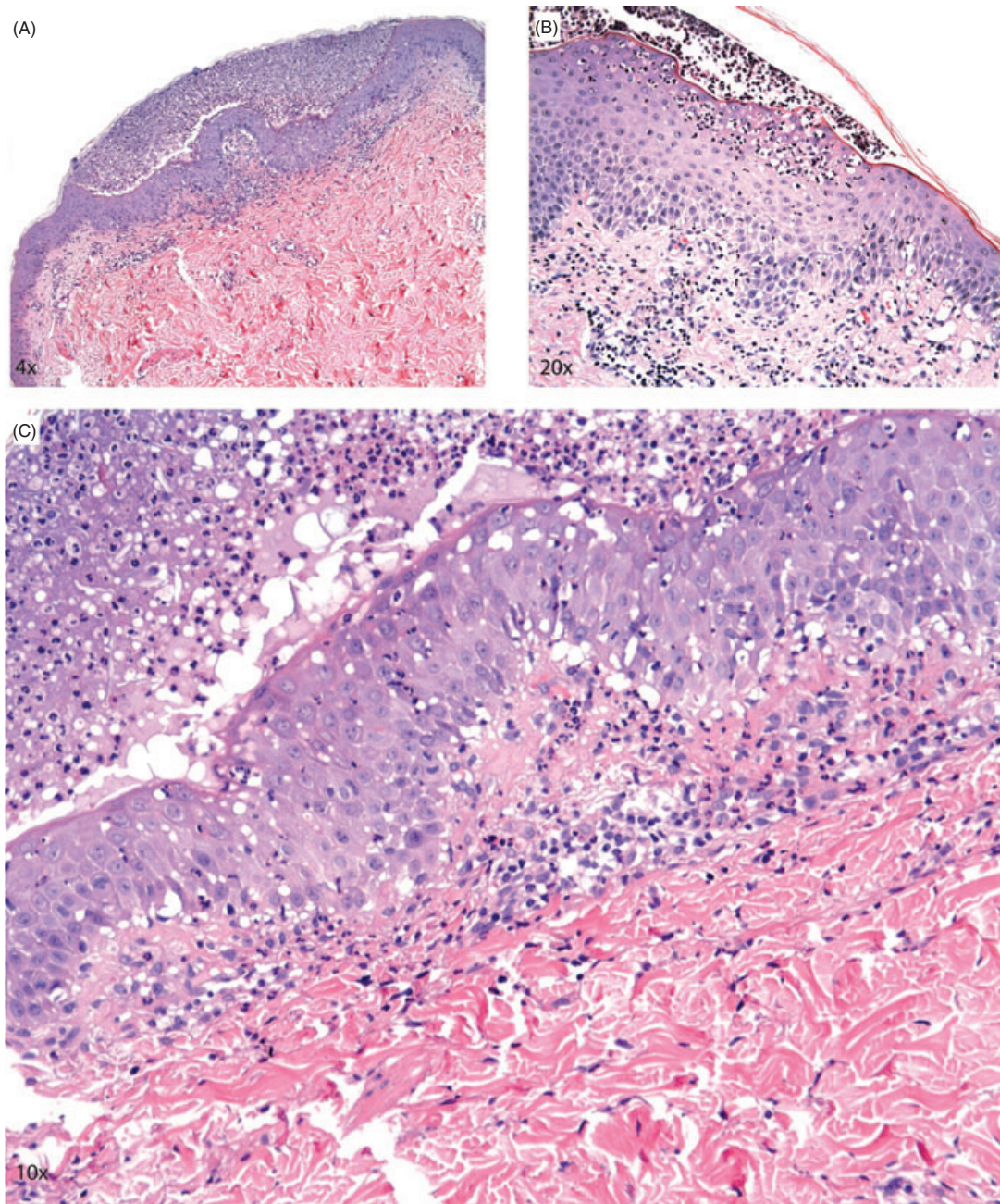
Comparison of 27 biopsies from pustules in AGEP with 14 biopsies of aGPP and 10 of cGPP showed several significant differences (Table 3). In GPP, pustules contained no eosinophils. Compared to AGEP, they generally contained more lysed keratinocytes and were more spongiform and were situated at a slightly higher epidermal level. Macro-pustules were prominent in GPP; in cGPP they were often situated at a more superficial epidermal level (Fig. 2A), while in aGPP they were often quite large (Fig. 3A). Psoriasiform epidermal changes were most prominent in cGPP (Fig. 2A,B). Most striking in GPP was the consistent presence of tortuous, dilated blood vessels (96%) (Figs. 2A,B and 3B). Compared with AGEP, necrotic keratinocytes

and dermal eosinophils were significantly less present in GPP. The infiltrate in GPP was mainly superficial, perivascular, less pronounced and mainly mononuclear, while in AGEP the infiltrate was also deeper and interstitial. Neutrophils in aGPP were markedly located in the papillary dermis in comparison to AGEP and cGPP (Fig. 3A–C).

Histopathology of a subgroup of seven AGEP patients with a personal history of psoriasis showed no significant differences with cases without pre-existing psoriasis. However, slight psoriasiform changes and presence of tortuous/dilated blood vessels were seen more often in this subgroup (Fig. 1D).

### Discussion

We believe that the strength of our study is the comparison of both AGEP and GPP by an identical



*Fig. 3.* Histopathology of acute generalized pustular psoriasis (aGPP). A) Subcorneal macro-pustule, neutrophilic exocytosis, superficial perivascular, mainly mononuclear, infiltrates with papillary neutrophils. B) Subcorneal/intraepidermal spongiform macro-pustule of Kogoj, neutrophilic exocytosis, slightly psoriasiform rete ridge changes and dilated papillary vessels. C) Detail macro-pustule: neutrophilic exocytosis, papillary neutrophils and superficial perivascular, mainly mononuclear infiltrate. Hematoxylin and eosin, original magnification: (A)  $\times 40$ , (B)  $\times 200$  and (C)  $\times 100$ .

set of histopathological parameters. Both AGEP and GPP represent a dynamic spongiotic pustular process. This presumably starts with dermal edema and a perivascular infiltrate, and this is followed by pustules in different stages of evolution. Because of this evolution, we studied the features of AGEP in erythema and visible pustules. While cGPP develops over time, aGPP represents acute pustule formation on previously uninvolved skin. Differential diagnostic

problems between AGEP and GPP particularly arise in the acute phase of GPP.

It is noteworthy that we found small pustules in all biopsies from erythematous lesions of AGEP. In aGPP, pustules were concentrated somewhat deeper in the epidermis than in cGPP. In biopsies from pustular lesions of AGEP, pustules of different sizes were distributed over several levels, probably reflecting the ongoing process with pustules at consecutive



stages in one biopsy. Subcorneal pustules, contiguous to intraepidermal ones, were markedly spongiform in AGEP but were generally less prominent than in GPP.<sup>4,19,20,24</sup> Differences in localization and spongiform character of pustules in a biopsy can provide a hint for differentiating AGEP from GPP. Although in AGEP, pustules were generally non-follicular, follicular pustules could sometimes be observed as well. In our experience, follicular pustules do not exclude the diagnosis of AGEP.

Munro micro-abscesses, representing collections of neutrophils within parakeratosis, are generally associated with psoriasis. However, in AGEP we also observed variously sized late-stage (dried) intracorneal pustules that assumed the configuration of Munro micro-abscesses. The higher frequency of Munro micro-abscesses and of other intracorneal pustules in cGPP can be explained by its more protracted course compared with AGEP or aGPP. Spongiform macro-pustules were dominantly present in GPP. Although generally associated with GPP and not with AGEP, those macro-pustules were also regularly (63%) observed in biopsies of AGEP when taken from pustular lesions.

Whether histopathological features of conventional plaque-type psoriasis can be seen in GPP is controversial.<sup>18,25,26</sup> Our study suggests that this controversy is mainly a matter of timing, because psoriatic changes such as hyperkeratosis, parakeratosis, a diminished stratum granulosum, rete ridge changes, elevated mitotic index and suprapapillary plate thinning were far more prominent in cGPP. We believe this is because of its more chronic stage in comparison with aGPP. In aGPP the epidermis was often only slightly acanthotic, as in AGEP. Absent or minor alterations of the stratum corneum, particularly in early lesions of AGEP but also in aGPP, indicate an acute process. Rete ridge change (such as elongation), generally mild, was more frequent in AGEP than generally reported and in our view is apparently less a key point in favor of GPP than previously assumed.<sup>11,18,19</sup> Alterations in rete ridge point to a more developed stage of lesion, since we found them more prominently in pustular than erythematous AGEP lesions (59%), especially when desquamating intracorneal pustules were present. Although substantial psoriasiform changes in a pustular lesion are suggestive of GPP, their absence (such as in aGPP) does not necessarily exclude GPP. On the other hand, minor psoriasiform changes do not rule out AGEP.

While tortuous, dilated vessels were expected in cGPP, we surprisingly also observed them significantly more in aGPP than in AGEP. Moreover, in AGEP they were strongly associated with cases having a personal history of psoriasis (data not shown).

Presumably vascular alterations are very specific for psoriasis and are widely present in patients with the disease.

Necrotic keratinocytes, also observed in other drug eruptions, were generally few or scattered outside the pustule in AGEP (88%), while in GPP we hardly found them.<sup>24</sup> On the other hand, lysed keratinocytes within the pustules were more pronounced in GPP, resulting in slightly more spongiform pustules, especially in aGPP.<sup>15,18,25</sup> In AGEP, apoptosis of activated keratinocytes is mainly caused by CD8+ lymphocytes, but CD4+ drug-specific cytotoxic T cells also play a role.<sup>27</sup>

Dermal edema is relatively characteristic (but not specific) for AGEP, especially in its early stages.<sup>16,20</sup> Although less marked than often suggested, moderate to severe papillary edema was present in 40% of biopsies from patients with AGEP, in 29% of biopsies from patients with aGPP and almost absent in biopsies from patients with cGPP.

Eosinophils in pustules, in the dermis and also in the peripheral blood, a hallmark of many drug-induced allergic reactions, suggests that AGEP is a hypersensitivity reaction.<sup>18,28</sup> Although the process of eosinophilic exocytosis was observed in just four biopsies (data not shown), sparse eosinophils were found in 58% of the pustules.<sup>4,16</sup> Dermal eosinophils were more frequent (95%) although less pronounced than sometimes reported.<sup>4,17,18,22–24</sup> In contrast to AGEP, eosinophils were only found sporadically in GPP.<sup>26</sup>

Remarkably, an interstitial and perivascular mid-dermal infiltrate is not generally considered a feature of AGEP. We found such an infiltrate to be pronounced and mixed, often including numerous neutrophils. In GPP, the infiltrate was less dense, was located more superficially and was mainly mononuclear, while neutrophils were found predominantly in the papillary dermis. We believe these differences in composition and distribution can be diagnostically meaningful.

We regularly noticed erythrocyte extravasation (not generally reported) and mild leukocytoclasia, but alterations suggesting possible vasculitis, including fibrin deposition in the vessel wall, was seen only once in AGEP. Absence of clear evidence for vasculitis in the presence of erythrocyte extravasation and leukocytoclasia has been mentioned before.<sup>20,21</sup> Acute vasculitis in AGEP is sometimes reported in a connection of subepidermal with intraepidermal pustules, which is something we did not observe.<sup>17,24</sup> Overreporting of vasculitis might be caused by interpretation of leukocytoclasia and/or erythrocyte extravasation as vasculitis or by diagnostic confusion with pustular vasculitis. Purpura may occur in

AGEP and other drug-induced eruptions, even in the absence of vasculitis.

An earlier clinical study of 63 cases of AGEP, including 64 biopsies from 48 patients, mentions superficial spongiform pustules (66%), focal necrotic keratinocytes (25%), psoriasiform hyperplasia (39%), mixed perivascular infiltrates with eosinophils (34%), papillary edema (61%) and leukocytoclastic vasculitis (20%) including fibrinoid changes (11%).<sup>16</sup> Remarkably, our study showed far more pustules, papillary edema (91%), dermal eosinophilia (95%) and necrotic keratinocytes (88%). This might indicate that biopsies in these two studies were taken at different stages. We found far less fibrinoid alteration, while psoriatic changes were comparable. Differences might also be attributed to case definition, inclusion criteria and use of step sections in our study.

AGEP can also occur in patients with plaque psoriasis. It has been suggested that AGEP merely represents a variant of GPP, and thus signifies an acute exacerbation of psoriasis caused by a variety of exogenous triggers. However, analysis of a subgroup of seven AGEP cases with a known personal history of psoriasis in our study did not show significant differences with the other cases. Also, the observation of several significant differences in GPP vs. AGEP supports the concept that AGEP is a separate entity that can occur as an acute eruption in patients with a history of psoriasis. On the basis of our findings, there are no grounds to assume that an acute pustular rash, occurring in patients with known psoriasis, is necessarily GPP or that AGEP is a variant of pustular psoriasis.

As noticed before, the prevalence of patients with a personal history of psoriasis in our study of AGEP (26.9%) was higher than could be expected from the general population (1–4%).<sup>3,5,16,29,30</sup> This higher prevalence might indicate that patients with GPP and AGEP share a common genetic background, which directs them to react with neutrophil-attracting mechanisms.

The etiopathogenesis of AGEP is still not fully elucidated although some progress has been made. Positive results from patch and lymphocyte transformation tests with the suspected agent, indicating a delayed type IV hypersensitivity reaction, support a drug etiology and the concept that T cells play a crucial role.<sup>21,31</sup> It was recently appreciated that interleukin-8 (IL-8), secreted by T cells and keratinocytes, enhances neutrophilic inflammation and survival, thus leading to sterile pustular lesions.<sup>31,32</sup> Similar mechanisms seem to be relevant for other T-cell-mediated diseases with neutrophilic inflammation, like GPP, which has an underlying tendency for a Th1-dominated immune response.<sup>32–35</sup> Besides,

few CXCL8+ T cells displaying a Th2-type cytokine profile with high IL-4 and IL-5 secretions, may contribute to the eosinophilia, regularly observed in AGEP.<sup>32</sup> In GPP, IL-5 is not secreted, which might explain the absence of eosinophilia.<sup>28,36</sup>

## Conclusions

In summary, the present study found a spectrum of histopathological features of both AGEP and GPP. Differentiating AGEP from GPP, especially aGPP, presents a clinical and histopathological challenge. Whereas no single histopathological feature is decisive on its own, the combination of features and their grade of severity can substantially contribute to negotiating this differential diagnosis successfully. Features pointing at AGEP instead of GPP include the presence of eosinophils in the pustules or dermis, necrotic keratinocytes, a mixed neutrophil-rich interstitial and mid-dermal infiltrate and the absence of tortuous, dilated blood vessels. Moreover, cGPP showed significant epidermal psoriasiform changes. These key histopathological features, combined with clinicopathological correlation, will assist in differentiation between AGEP and GPP in most instances.

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