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# Severe acute generalized exanthematous pustulosis with toxic epidermal necrolysis-like desquamation: A case series of 8 patients

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***Key words:*** acute generalized exanthematous pustulosis; AGEP; case series; SCAR; severe cutaneous adverse drug reaction; SJS; Stevens-Johnson syndrome; TEN; toxic epidermal necrolysis.

## INTRODUCTION

Acute generalized exanthematous pustulosis (AGEP) is a severe cutaneous adverse reaction (SCAR) with heterogeneous clinical and histopathologic features. Notably, extensive cases of AGEP can show overlapping features with toxic epidermal necrolysis (TEN) by presenting with widespread desquamation and necrotic keratinocytes on histopathology. AGEP classically appears with superficial nonfollicular pustules on an erythematous background beginning in intertriginous areas; it is characterized by intradermal, subcorneal, and intracorneal pustules with frequent spongiform changes on histopathology.[1] In contrast, TEN presents with a painful desquamative rash that starts as dusky erythematous macules, generally involving the mucosal membranes and covering >30% of the body surface area. Histopathology shows an interface dermatitis with keratinocyte necrosis, which can progress to full-thickness epidermal necrolysis and separation from the dermis.[2] Although classic AGEP differs from TEN by clinical appearance and histopathologic findings, cases with overlapping features have rarely been reported in the literature.[3] Importantly, distinguishing severe AGEP from TEN is essential due to differences in prognosis and management. We present a case series of AGEP with TEN-like desquamation and highlight important clues in identifying severe and atypical cases of AGEP.

*Abbreviations used:*

| | |
|---|---|
| AGEP: | acute generalized exanthematous pustulosis |
| IL-8: | interleukin 8 |
| SCAR: | severe cutaneous adverse reaction |
| TEN: | toxic epidermal necrolysis |

## CASE SERIES

A chart review of 8 patients with extensive AGEP was performed by 2 evaluators (K.M. and S.H.; Table I). Analysis of their clinical and histopathologic findings highlights essential features that help in correctly diagnosing AGEP (Figs 1-5; Supplemental Figs 1 to 3 available via Mendeley at https://data.mendeley.com/datasets/cgfm69xhnh/1). All cases scored a minimum of 6, using the EuroSCAR criteria for diagnosis of AGEP (Table II), with 2 cases classified as "probable AGEP" and 6 cases classified as "definite AGEP."[4]

All patients were seen as hospital dermatology consults. Initial differential diagnoses included TEN, AGEP, staphylococcal scalded skin syndrome, and/or toxic shock syndrome. The data from Table I show that all cases ($n$ = 8) presented with widespread desquamation covering more than 50% of the body surface area. Only 1 case ($n$ = 1) presented with typical AGEP pustules on clinical examination. Pain with desquamation was observed in 1 patient ($n$ = 1). Mucosal involvement was seen in 1 patient ($n$ = 1). Four patients ($n$ = 4) presented with a fever of >38 °C. All patients presented with neutrophilia (>7000 neutrophils/mm$^3$). Antibiotics ($\beta$-lactams, $n$ = 5; clindamycin, $n$ = 1; vancomycin, $n$ = 1) and calcium channel

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**Table I.** Spectrum of clinical and histopathologic findings in 8 patients with severe acute generalized exanthematous pustulosis clinically mimicking toxic epidermal necrolysis*

| Parameter | Case 1 | Case 2 | Case 3 | Case 4 | Case 5 | Case 6 | Case 7 | Case 8 |
|---|---|---|---|---|---|---|---|---|
| Clinical features† | | | | | | | | |
| Initial diagnosis | TEN vs AGEP | TEN vs AGEP | TSS vs SSSS vs TEN | TEN | TSS vs SSSS vs TEN | TEN | TEN vs SSSS | TEN |
| Estimated percentage body surface area involvement | 50 | 50 | 90 | 60 | 100 | 80 | 80 | 100 |
| Pustules | Compatible | Typical | Compatible | Compatible | Compatible | Compatible | Compatible | Compatible |
| Erythema | Compatible | Compatible | Compatible | Compatible | Compatible | Compatible | Compatible | Compatible |
| Distribution | Typical | Compatible | Compatible | Compatible | Compatible | Compatible | Compatible | Compatible |
| Postpustular desquamation | + | + | + | + | + | + | + | + |
| Mucosal involvement | − | − | − | + | − | − | − | − |
| Acute onset (<10 d) | + | + | + | + | + | + | + | + |
| Resolution (<15 d) | + | + | + | + | + | + | + | + |
| Fever (≥38 °C) | − | + | + | + | + | − | − | − |
| Neutrophil count (≥7000/mm$^3$) | + | + | + | + | + | + | + | + |
| Implicated drug | Diltiazem | Piperacillin-tazobactam | Cefepime | Cephalexin | Cephalexin | Clindamycin | Vancomycin | Cefepime |
| Treatment | Prednisone taper | Intravenous immunoglobulin (administered prior to diagnosis) | Wound care | Prednisone | Emollient only | Emollient only | Wound care | Topical steroids |
| EuroSCAR score | 6 | 10 | 9 | 7 | 8 | 8 | 8 | 8 |
| Histology | | | | | | | | |
| Frozen histology | − | Intraepidermal pustules with keratinocyte necrosis | Intraepidermal pustules with keratinocyte necrosis | − | − | Neutrophilic spongiosis and parakeratosis but no necrosis | Neutrophilic spongiosis with widespread keratinocyte necrosis | Neutrophilic spongiosis with widespread keratinocyte necrosis |
| Subcorneal pustule | − | + | + | + | + | + | + | + |
| Intraepidermal pustule | − | + | + | − | − | − | − | + |
| Spongiform pustule | − | + | + | + | − | + | + | + |

| | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| Spongiosis | Focal | Extensive spongiosis forming intraepidermal bullae with exocytosis of N/E/L | Extensive spongiosis forming intraepidermal bullae with exocytosis of N/E/L | Focal with exocytosis of N/L | Focal with exocytosis of N | Focal | Focal | Extensive spongiosis |
| Psoriasiform hyperplasia | + | − | − | − | − | − | + | − |
| Parakeratosis | Focal | − | − | − | + | + | + | + |
| Papillary dermal edema | Mild | Significant | Significant | Significant | Mild | Mild | Significant | Significant |
| Subepidermal cleft | − | − | − | − | − | − | − | − |
| Keratinocyte necrosis | None | Many | Many | None | Rare | None | Many | Many |
| Dermal infiltrate | Superficial perivascular infiltrate with L | Superficial and deep perivascular/periadnexal infiltrates, mixed N/E/L | Superficial and deep perivascular infiltrates, mixed N/E/L | Superficial and deep perivascular/periadnexal infiltrates, mixed N/L | Superficial and deep perivascular infiltrates, mixed N/E/L | Superficial perivascular infiltrates, mixed N/L | Superficial perivascular infiltrates, mixed N/L | Superficial and deep perivascular infiltrates, mixed N/L |

*AGEP*, Acute generalized exanthematous pustulosis; *E*, eosinophils; *L*, lymphocytes; *N*, neutrophils; *SSSS*, staphylococcal scalded skin syndrome; *TEN*, toxic epidermal necrolysis; *TSS*, toxic shock syndrome.

*EuroSCAR score interpretation: 0, no AGEP; 1 to 4, possible AGEP; 5 to 7, probable AGEP; 8 to 12, definite AGEP.

†Classification of morphology defined by the EuroSCAR criteria is as follows: ''Typical''—typical morphology (many small, <5 mm, nonfollicular pustules on background edematous erythema, predilection for intertriginous areas); ''Compatible''—not typical, but not strongly suggestive of other disease; and ''Insufficient''—lesions cannot be judged (due to late stage of lesions or poor quality of images).

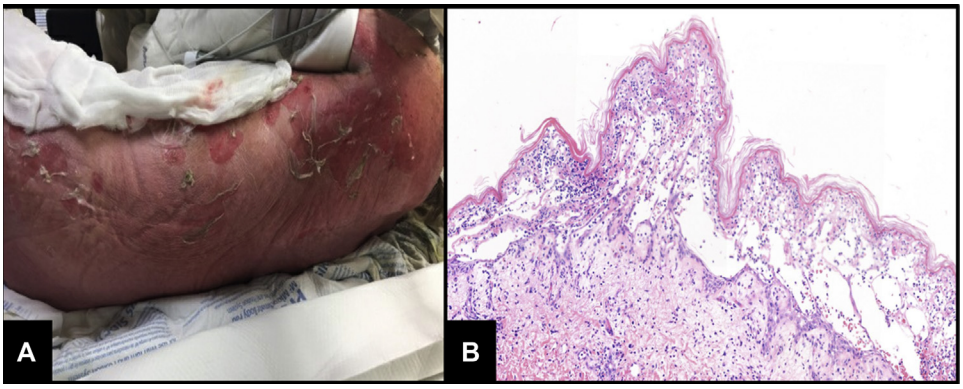


**Fig 1. A**, Patient 3 presented with sheets of desquamation, flaccid bullae, and wet, erythematous denuded skin. **B**, Punch biopsy showed extensive neutrophilic spongiosis with necrotic keratinocytes. (**B**, Hematoxylin-eosin stain; original magnification: **B**, ×40.)

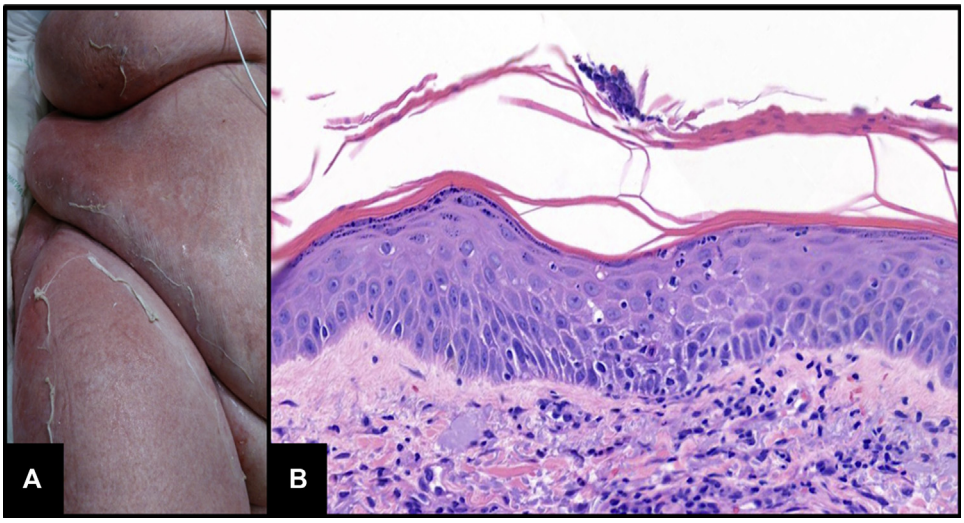


**Fig 2. A**, Patient 5 presented with large sheets of superficial desquamation without identifiable pustules. **B**, Punch biopsy showed mild spongiosis with neutrophilic exocytosis and intracorneal pustules. (**B**, Hematoxylin-eosin stain; original magnification: **B**, ×100.)

blockers ($n$ = 1) comprised the suspected triggers. The average time to onset of rash was 3.1 days, and average time to resolution was 6.8 days. Administered treatment included wound care and topical steroids ($n$ = 5), prednisone taper ($n$ = 2), and intravenous immunoglobulin ($n$ = 1).

On histopathology, the classic AGEP finding of subcorneal/intraepidermal pustules was observed in most cases ($n$ = 7). Other common findings were spongiosis ($n$ = 8), papillary dermal edema ($n$ = 8), and a superficial perivascular inflammatory infiltrate ($n$ = 8). Features overlapping with TEN, such as keratinocyte necrosis (rare, $n$ = 1; segmental, $n$ = 4) and dermal eosinophils ($n$ = 3), were also observed. Of the 5 frozen sections, 4 showed necrotic keratinocytes ($n$ = 4).

## DISCUSSION

Correct identification of severe cases of AGEP can be difficult due to a confluence of pustules leading to large sheets of superficial desquamation. These cases may be underreported and misdiagnosed as TEN due to shared clinical and histopathologic features. We present 8 cases of AGEP with TEN-like desquamation and an initial differential diagnosis that included TEN. Cases were defined as AGEP by the EuroSCAR criteria, a validation metric for the correct diagnosis of AGEP. Cases are scored as "not," "possible," "probable," and "definite" AGEP. Grading parameters include lesion morphology, course of disease, and histopathologic features (Table II).[4] TEN-like AGEP has been reported in the literature and its differentiation from actual TEN is critical to avoiding overtreatment.[3]

**Table II.** Features of acute generalized exanthematous pustulosis graded by EuroSCAR criteria[4]*

| Features | Grading |
|---|---|
| Morphology | |
| Pustules | Typical†: +2; Compatible‡: +1; Insufficient§: 0 |
| Erythema | Typical: +2; Compatible: +1; Insufficient: 0 |
| Distribution | Typical: +2; Compatible: +1; Insufficient: 0 |
| Postpustular desquamation | Yes: +1; No: 0 |
| Course | |
| Mucosal involvement | Yes: −2; No: 0 |
| Acute onset (≤10 d) | Yes: 0; No: −2 |
| Resolution (≤15 d) | Yes: 0; No: −4 |
| Fever (≥38 °C) | Yes: +1; No: 0 |
| Neutrophilia (≥7000/mm$^3$) | Yes: +1; No: 0 |
| Histopathology | |
| Other disease | −10 |
| Not representative/no histology | 0 |
| Exocytosis of neutrophils | +1 |
| Subcorneal and/or intraepidermal nonspongiform or NOS pustules with papillary edema or subcorneal and/or intraepidermal spongiform or NOS pustules without papillary edema | +2 |
| Spongiform subcorneal and/or intraepidermal pustules with papillary edema | +3 |

*NOS*, Not otherwise specified.
*Interpretation: ≤0, no acute generalized exanthematous pustulosis (AGEP); 1 to 4, possible AGEP; 5 to 7, probable AGEP; 8 to 12, definite AGEP.
†Typical: Typical morphology with many nonfollicular sterile pustules arising on edematous erythema mainly in intertriginous areas.
‡Compatible: Not typical but not strongly suggestive of other disease.
§Insufficient: Lesions cannot be judged (mostly because of late of the disease or poor quality of pictures).

Classically, AGEP is characterized by numerous sterile, nonfollicular pustules on background erythema, but these are often missing when extensive desquamation occurs. However, other features can help clue the clinician into the diagnosis. Typically, the desquamation in AGEP is more superficial than that observed in TEN. However, clinical examination cannot always reliably distinguish the level of split as seen in cases 3 and 8. Histopathologic examination for these 2 cases showed significant neutrophilic spongiosis causing an intraepidermal sloughing a few cells above the basal layer, explaining the difficulty in clinical discrimination from the subepidermal split seen in TEN (Figs 1 and 5). Furthermore, AGEP typically lacks the extensive mucous membrane involvement observed in TEN.[4] Mucosal involvement is seen in >90% of patients with TEN, with a study showing 81% of patients with involvement of 2 or more mucous membranes.[5] Our case series included 1 patient with mucous membrane involvement. Additionally, patients with AGEP are less likely to have pain with desquamation compared with patients with TEN. Only patient 7 responded with pain upon palpation of her rash.

Per EuroSCAR criteria, laboratory values showing peripheral neutrophilia (≥7000/mm$^3$) and fever (≥38 °C) are features of classic AGEP, albeit they are not specific for this particular drug reaction.[1] Significant internal organ involvement is infrequent, although lymphadenopathy and mild-to-moderate aberrations in hepatic aminotransferases and creatinine clearance can be observed.[4] In 1 retrospective study, 10/58 AGEP patients developed at least 1 systemic involvement (hepatic, renal, or pulmonary).[6]

Both AGEP and TEN are commonly attributed to drug reactions. AGEP has been associated with aminopenicillins, pristinamycin, macrolides, quinolones, hydroxychloroquine, antifungal agents, and diltiazem.[7] TEN has been linked to an extensive list of medications; most commonly allopurinol, trimethoprim-sulfamethoxazole and other sulfonamide antibiotics, aminopenicillins, cephalosporins, quinolones, phenobarbital, nonsteroidal antiinflammatory drugs, and anticonvulsants such as carbamazepine, lamotrigine, and phenytoin.[2]

The onset, progression, and prognosis help to differentiate the 2 conditions. AGEP is more acute in onset, as it typically occurs hours to days after starting the drug, and TEN generally occurs 1 to 3 weeks after the inciting medication. Withdrawal of the trigger drug leads to faster resolution in AGEP (several days to 1 week) compared to that of TEN (1-3 weeks or longer for extensive mucosal involvement).[3] Our cases resolved in 6.8 days on average,

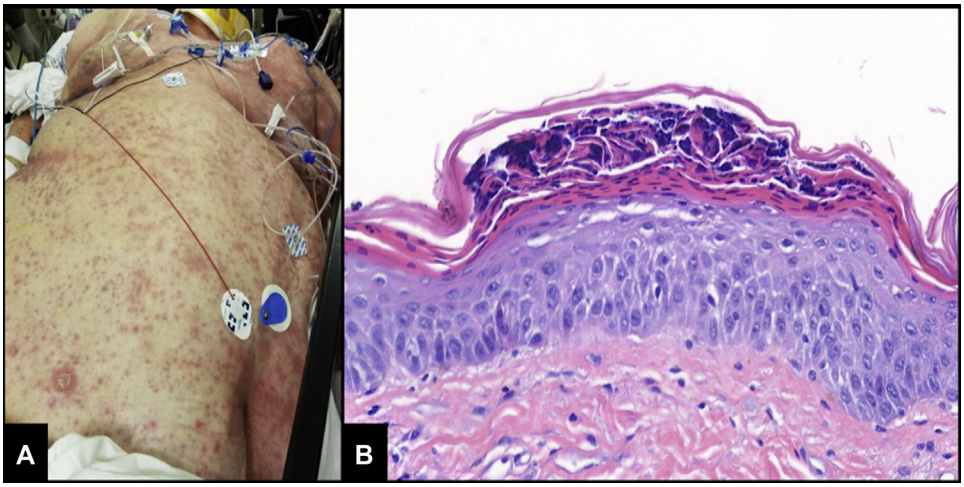


**Fig 3.** **A**, Patient 6 presented with extensive erythematous macules that coalesced into large patches with superficial desquamation. **B**, Punch biopsy showed spongiosis with subcorneal pustules. (**B**, Hematoxylin-eosin stain; original magnification: **B**, ×100.)

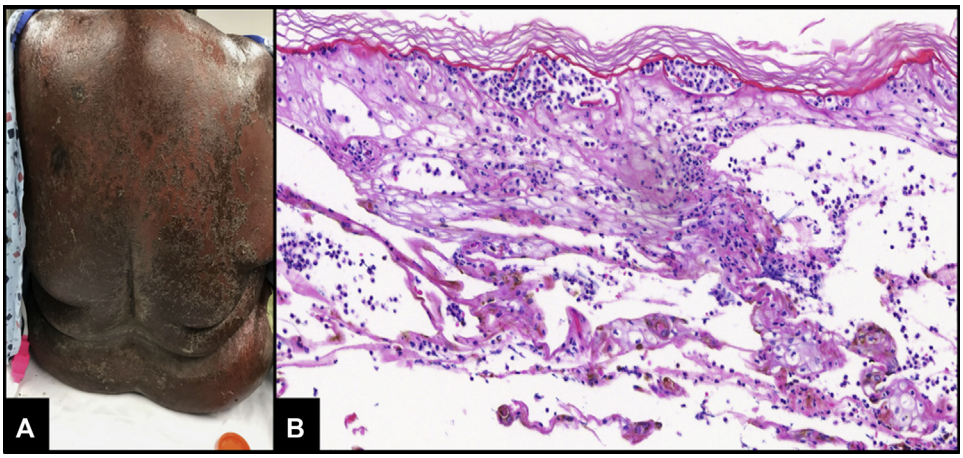


**Fig 4.** **A**, Patient 7 presented with large areas of dry desquamation on the back and flaccid bullae on the chest and extremities. **B**, Punch biopsy showed subcorneal pustules, significant neutrophilic spongiosis, and necrotic keratinocytes. (**B**, Hematoxylin-eosin stain; original magnification: **B**, ×20.)

with all cases resolving before the 15-day cutoff used by EuroSCAR criteria. The mortality rate is significantly higher in TEN, with TEN having an estimated mortality of 30% or higher.[8] Clinical comorbidities are significant, including long-term ocular complications and persistent mucosal lesions. In contrast, AGEP is generally self-limiting, and resolution of lesions occurs within 1 to 2 weeks following drug withdrawal.[1,6] Mortality is less than 5% in AGEP with few lasting comorbidities.[1]

AGEP has several histopathologic features, including spongiform subcorneal or intraepidermal pustules, a mixed perivascular and interstitial infiltrate +/- eosinophils, papillary dermal edema, psoriasiform hyperplasia, and focal keratinocyte necrosis. The clinical differential diagnosis includes pustular psoriasis, subcorneal pustular dermatosis, staphylococcal scalded skin syndrome, TEN, and drug hypersensitivity syndrome. On histopathology, pustular psoriasis may most commonly share features with AGEP. Histopathologic similarity with TEN has also been reported.[9]

TEN is characterized by keratinocyte necrosis with full-thickness epidermal necrolysis, a sparse mixed inflammatory infiltrate, and subepidermal bullae formation on histopathology.[2] However, epidermal necrosis and subepidermal bullae have also been reported in AGEP.[9] One study showed scattered or segmental necrotic keratinocytes in 46% and 7% of AGEP cases, respectively.[10] Our case

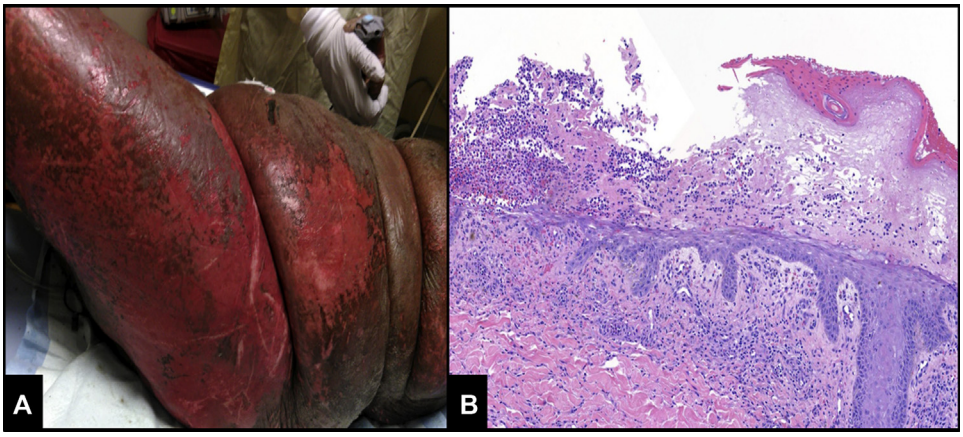


**Fig 5. A**, Patient 8 presented with bright red, raw-appearing erosions on the trunk and extremities with dried, flaking skin and hemorrhagic crust on the head and neck. **B**, Punch biopsy showed extensive neutrophilic spongiosis, papillary dermal edema, and necrotic keratinocytes. (**B**, Hematoxylin-eosin stain; original magnification: **B**, ×100.)

series showed significant keratinocyte necrosis in 4 of the 8 patients. The higher proportion of cases with segmental necrotic keratinocytes on histopathology likely reflects the selection bias of clinically severe AGEP cases.

In the case series, 4 of the 5 frozen sections showed necrotic keratinocytes. Frozen section is a valuable, yet underutilized tool for rapid inpatient diagnosis of SCARs. It is especially useful in diagnosing Stevens-Johnson syndrome/TEN, with epidermal necrosis being a characteristic feature.[11] However, a singular focus on necrotic keratinocytes can lead to a misdiagnosis of Stevens-Johnson syndrome/TEN in cases of severe AGEP where significant necrosis is possible. Frozen sections from epidermis-only biopsies only further compound this problem by providing partial sampling. Consideration of EuroSCAR criteria such as clinical onset/resolution of rash and lesion morphology can help avoid this important diagnostic pitfall when performing frozen sections for the rapid diagnosis of SCARs; epidermal necrosis is not specific for TEN.

Although AGEP can present with features of TEN, they are separate conditions with distinct etiologies. AGEP occurs due to interleukin 8 (IL-8) recruitment and activation of neutrophils as a type IVd T-cell reaction, whereas TEN is a type IVc reaction, in which cytotoxic $CD8^+$ T cells cause keratinocyte apoptosis.[12] Inflammatory skin reactions occur when drug-specific T cells cause the release of granulysin in TEN, and IL-8, interleukin 17, and interleukin 22 in AGEP.[13] Overlap between these immune reactions may explain the presence of features of TEN in AGEP cases.

Severe cases of AGEP may share clinical and histopathologic features with TEN. However, in our case series, superficial desquamation, the absence of severe mucosal involvement, rapid onset/resolution of rash, lack of pain with desquamation, and the presence of neutrophilic spongiform pustules with dermal edema on histopathology favored a diagnosis of AGEP. Using EuroSCAR criteria can help narrow the diagnosis, with all 8 cases scoring as "probable" or "definite" AGEP. Cases of AGEP with TEN-like desquamation represent a distinct morphological presentation of AGEP that should be recognized to avoid misdiagnosis and mistreatment.

### Conflicts of interest

None disclosed.

### REFERENCES

1. De A, Das S, Sarda A, Pal D, Biswas P. Acute generalised exanthematous pustulosis: an update. *Indian J Dermatol*. 2018; 63(1):22-29. https://doi.org/10.4103/ijd.IJD_581_17
2. Harr T, French LE. Toxic epidermal necrolysis and Stevens-Johnson syndrome. *Orphanet J Rare Dis*. 2010;5:39. https://doi.org/10.1186/1750-1172-5-39
3. Copaescu AM, Bouffard D, Masse MS. Acute generalized exanthematous pustulosis simulating toxic epidermal necrolysis: case presentation and literature review. *Allergy Asthma Clin Immunol*. 2020;16:9. https://doi.org/10.1186/s13223-020-0407-5
4. Sidoroff A, Halevy S, Bavinck JN, Vaillant L, Roujeau JC. Acute generalized exanthematous pustulosis (AGEP)—a clinical reaction pattern. *J Cutan Pathol*. 2001;28(3):113-119. https://doi.org/10.1034/j.1600-0560.2001.028003113.x
5. Wetter DA, Camilleri MJ. Clinical, etiologic, and histopathologic features of Stevens-Johnson syndrome during an 8-year period at Mayo Clinic. *Mayo Clin Proc*. 2010;85(2):131-138. https://doi.org/10.4065/mcp.2009.0379
6. Hotz C, Valeyrie-Allanore L, Haddad C, et al. Systemic involvement of acute generalized exanthematous pustulosis: a retrospective study on 58 patients. *Br J Dermatol*. 2013; 169(6):1223-1232. https://doi.org/10.1111/bjd.12502
7. Feldmeyer L, Heidemeyer K, Yawalkar N. Acute generalized exanthematous pustulosis: pathogenesis, genetic background,

clinical variants and therapy. *Int J Mol Sci*. 2016;17(8):1214. https://doi.org/10.3390/ijms17081214

8. Bastuji-Garin S, Fouchard N, Bertocchi M, Roujeau JC, Revuz J, Wolkenstein P. SCORTEN: a severity-of-illness score for toxic epidermal necrolysis. *J Invest Dermatol*. 2000;115(2):149-153. https://doi.org/10.1046/j.1523-1747.2000.00061.x
9. Goh TK, Pang SM, Thirumoorthy T, Goh SGN. Acute generalised exanthematous pustulosis and toxic epidermal necrolysis induced by carbamazepine. *Singapore Med J*. 2008;49(6):507-510.
10. Halevy S, Kardaun SH, Davidovici B, Wechsler J, EuroSCAR, RegiSCAR study group. The spectrum of histopathological features in acute generalized exanthematous pustulosis: a study of 102 cases. *Br J Dermatol*. 2010;163(6):1245-1252. https://doi.org/10.1111/j.1365-2133.2010.09967.x
11. Hosaka H, Ohtoshi S, Nakada T, Iijima M. Erythema multiforme, Stevens-Johnson syndrome and toxic epidermal necrolysis: frozen-section diagnosis. *J Dermatol*. 2010;37(5):407-412.
12. Peermohamed S, Haber RM. Acute generalized exanthematous pustulosis simulating toxic epidermal necrolysis: a case report and review of the literature. *Arch Dermatol*. 2011;147(6):697-701. https://doi.org/10.1001/archdermatol.2011.147
13. Bouvresse S, Valeyrie-Allanore L, Ortonne N, et al. Toxic epidermal necrolysis, DRESS, AGEP: do overlap cases exist? *Orphanet J Rare Dis* 2012;7:72. https://doi.org/10.1186/1750-1172-7-72