

Acute generalized exanthematous pustulosis: 15-year retrospective multicenter experience

Running head: AGEP: 15-year experience

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Funding sources: This research received no specific grant from any funding agency in the public, commercial, or not-for-profit sectors.

Conflicts of interest: None to declare.

Data availability: The data underlying this article will be shared on reasonable request to the corresponding author.

Ethics statement: Not applicable.

Patient consent: Written patient consent for publication was obtained.

What is already known about this topic?

- Acute generalized exanthematous pustulosis (AGEP) is a rare severe cutaneous adverse reaction, generally related to drug intake. A prevalence of AGEP in adults and female sex, as well as β -lactam antibiotics as the main causative drugs have been described.

What does this study add?

- LDH may be proposed as a biomarker contributing to AGEP score.
- Histopathological examination revealed the presence of spongiform pustules, eosinophils, neutrophilic exocytosis, and spongiosis as the most frequent findings in AGEP.

1 **Abstract**

2 Background: Acute generalized exanthematous pustulosis (AGEP) is a rare skin condition often
3 triggered by medications. Many case reports have been published but a few studies on large cohorts
4 have been reported to date.

5 Objectives: The aim of the current study is to provide correlation between AGEP EuroSCAR score and
6 clinical, laboratory findings and histopathologic examination in a large cohort.

7 Methods: This retrospective, multicenter study analyzed 51 AGEP cases across four academic
8 institutions.

9 Results: The study found that the majority of cases were drug-induced, particularly by antibiotics such
10 as amoxicillin. The average time from drug exposure to symptom onset was 10.7 days, with
11 hospitalization lasting an average of 14.5 days and recovery averaging 33.3 days. Key features included
12 widespread itching, fever, and elevated inflammatory markers. Histopathological analysis frequently
13 revealed spongiform pustules and eosinophilic infiltration. Importantly, this study is the first to
14 demonstrate a significant association between higher EuroSCAR scores and elevated LDH levels,
15 suggesting a more intense inflammatory response in cases with higher EuroSCAR scores. The findings
16 underscore the need for early diagnosis and management of AGEP, with a particular focus on
17 discontinuing the offending drug and administering corticosteroids.

18 Conclusions: Despite its retrospective design, this study contributes valuable insights into the systemic
19 implications and histopathological characteristics of AGEP, highlighting the possible role of LDH, and
20 the importance of further research to refine diagnosis, treatment protocols and improve patient
21 outcomes.

1 Introduction

2 Acute generalized exanthematous pustulosis (AGEP) is a skin condition characterized by the
3 appearance of sterile, non-follicular pustules arising on large areas of oedematous erythema, involving
4 major intertriginous zones, trunk, and upper extremities (Figure 1).¹ Despite being rare, a possible
5 systemic involvement (including hepatitis, nephritis, or pneumonitis) can occur.²
6 AGEP are considered a severe cutaneous adverse reaction (SCAR) mediated by type IV immune
7 response to medications and the most common drugs involved are antibiotics. Other causes for AGEP
8 have been described such as infections or idiopathic cases.^{3,4}
9 The incidence of AGEP is low, with fewer than ten cases per million inhabitants per year, with a low
10 risk of mortality (1- 4%).^{1,5-8} Accordingly, AGEP is considered a cutaneous adverse reaction less
11 severe than Stevens Johnson syndrome, toxic epidermal necrolysis, and Drug Reaction with
12 Eosinophilia and Systemic Symptoms (DRESS) syndrome, but overlap cases have been described.^{5,9}
13 In the absence of specific tests, diagnosis is based on clinical appearance, laboratory tests and
14 histopathology.⁷ The histology of AGEP reveals neutrophil infiltrates, with a spongiform or
15 nonspongiform pattern, giving rise to subcorneal or intraepidermal pustules, with or without dermal
16 oedema, eosinophil infiltrates, necrotic keratinocytes, and mixed dermal and interstitial infiltrates.^{5,10}
17 However, plenty of case reports have been reported while only a few large case series are available in
18 the current literature.^{3,5,8,11-14}
19 The aim of the current study is to present a retrospective, multicenter series of AGEP cases, providing
20 correlation between AGEP EuroSCAR score and clinical, laboratory findings and histopathologic
21 examination.

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Materials and methods

Population

This was a retrospective case series using medical records conducted, between 2008 and 2023 at 4 academic/hospital institutions: 11 cases from Allergology and Immunology of Niguarda Ca' Granda Hospital, Milano, Italy; 27 cases from Dermatology of Policlinico Universitario of Milano, Italy; 1 case from Dermatology of San Raffaele Hospital, Milano, Italy; 12 cases from Pathology of Hospital Universitari General de Catalunya, Barcelona, Spain. All cases were scored according to the EuroSCAR scoring system, into possible (1-4), probable (5-7) and definite (8-12) cases of AGEP, and those with a score of at least 5 were included in the study.¹⁵

Data collection

Data retrieved included demographic data, ethnicity, medical history, previous SCAR, any previous allergy, suspected drug, latency between drug and AGEP, time course, body surface area (BSA) affected, complications, systemic involvement. Additionally, results of blood tests (blood count, Erythrocyte Sedimentation Rate (ESR), C-Reactive Protein (CRP), Lactate Dehydrogenase (LDH), as well as creatinine, estimated Glomerular Filtration Rate (eGFR), AST (aspartate aminotransferase), ALT (alanine transaminase), GGT (gamma-glutamyl transferase), ALP (alkaline phosphatase)) and histologic parameters were collected, when available. Treatment modality and follow-up were also considered and analyzed.

Statistical analysis

Statistical analyses were performed with SPSS software version 24.0 (Armonk, N.Y., US). Quantitative variables were expressed as mean +/- standard deviation (SD) (range) and compared with T-student's

test while qualitative variables were expressed as absolute number and relative percentage frequency and were compared with Pearson χ^2 test (for values <5 in the table of contingency, exact test of Fisher was applied). The mean value of EuroSCAR score was considered a cut-off to test possible correlation between demographic, clinical, blood tests and histopathology and AGEF EuroSCAR score. Significant variables (continuous variables were considered dichotomous according to mean values of each variables as cut-offs) in the univariate analysis were put into a multivariate analysis, and a regression logistic model with stepwise approach was employed. Sensitivity and specificity were calculated for predicting higher EuroSCAR score. Furthermore, the receiver operating characteristic (ROC) curve was constructed and the area under the curve (AUC) obtained. A p-value ≤ 0.05 was considered significant.

Results

Baseline characteristics

A total of 51 patients, of which 27 (53%) females, were included in the current study. The mean age was 61.8 ± 18.6 (range 1-93), with two pediatric cases of 1 and 10-year-old (Table 1). Most of the patients were Caucasians (92%) while the remnant 8% was represented by Asians, Americans and Africans.

Major part of patients ($n = 33$, 65%) had at least one comorbidity, in most cases represented by cardiovascular diseases ($n = 21$, 54%), neoplastic conditions ($n = 10$, 26%). A total of 18% of patients ($n = 7$) had a history of psoriasis.

Suspected causative agent

Suspected causative agent was identified in 43 patients (84% of cases), with 40 cases related to drugs, 1 case to contrast agent and one to supplements. In addition, one case was associated to covid-19 infection and flurbiprofen treatment administered during the week previous to AGEF development.

1 In most cases (n=15), antimicrobials were the culprit drugs, with amoxicillin being involved in 8 cases,
2 other penicillin-derivatives in 4 cases, fluoroquinolones in 4 cases. Other common drug classes
3 represented were antimalarials, xanthine oxidase inhibitors, non-steroidal anti-inflammatory drugs and
4 antivirals (Table 1).

5 6 Clinical course

7 Ninety percent of cases showed a EuroSCAR score between 8 and 12, including two cases in which
8 histology identified a potential differential diagnosis between AGEP and DRESS in one, and AGEP
9 and Sneddon-Wilkinson in the other. Following clinicopathologic correlation, both cases were
10 reclassified as AGEP. Eight patients had a previous history of drug reactions, including urticaria-
11 angioedema in 6 cases, 1 case of purpuric eruption and one previous case of exanthema. Notably, no
12 patients had a documented history of AGEP.

13 Latency of cutaneous symptoms was 10.7 ± 11.7 days (range 0-50), while length of hospitalization was
14 14.5 ± 11.8 days (1-60), with an estimated AGEP duration of 33.3 ± 4.9 days (5-180).

15 Mean body surface area (BSA) was 33.7 ± 24.1 (5-95) and mucosae were affected in 3 patients. Itch
16 was largely present in 92% of patients while fever was registered in 44% of patients. Systemic
17 involvement was registered in 5 patients for kidney and 3 for liver dysfunction. Mean EuroSCAR was
18 9.5 and mortality rate observed in our population was 0 (Table 1).

19 20 Blood tests

21 Results of blood tests were available for hospitalized patients, 39 patients out of 51. Overall, increased
22 level of ESR, CRP, WBC and LDH were registered (Table 1).

Histopathology

Histopathology was available for 45 cases (88%) (Table 2). Spongiform and/or subcorneal pustules and eosinophils were represented in more than 80% of cases, while spongiosis, exocytosis of neutrophils and neutrophils in dermis were represented in more than 70% of patients.

Correlation between EuroSCAR , clinical, laboratory and histopathologic features

A total of 18 patients had a EuroSCAR <9.5 and 21 had >9.5. Factors significantly associated with EuroSCAR in the univariate analysis were fever, LDH, creatinine and eGFR. Specifically, fever is a parameter included in EuroSCAR estimation, and it was represented in 61.9% of cases with increased EuroSCAR , as compared to 22% of patients with a lower EuroSCAR ($p=0.023$) while LDH was 272.8 ± 65 (range 150-392) in patients with increased EuroSCAR , as compared with 174.2 ± 42.6 (148-238), registered in patients with lower EuroSCAR ($p=0.013$) (Table 3). Lower creatinine and higher eGFR were significantly associated with EuroSCAR >9.5 (0.021 and 0.030, respectively). According to multivariate analysis, the only variable significantly associated with higher EuroSCAR scores was LDH (OR 1.035, 95% confidence interval 1.002-1.07, $p=0.039$). Sensitivity was 69.2% and specificity was 100%. AUC was 0.846 (Supplementary Fig 1).

No significant association were observed between EuroSCAR and histopathologic characteristics (data not shown).

Management

Systemic treatment, including corticosteroids and antihistamines, was performed in 33 patients while 27 were managed with topical drugs, mainly topical steroids. One patient was prescribed only emollients. A combined, systemic and topical, treatment was considered in 19 cases.

Discussion

Our study included 51 patients affected by AGEP, making it one of the largest patient cohorts in recent years.¹⁶ In our patient cohort, both males ($n = 24$) and females ($n = 27$) were nearly equally affected, with a slight female predominance (male/female ratio of 0.88), and a mean age of onset of 61.8 ± 18.65 years (range 1-93), consistent with previous studies.^{5,8}

Cardiovascular ($n = 21$) and oncological ($n = 10$) comorbidities were most common, consistent with the age of patients and general epidemiology. Psoriasis was more frequent than expected ($n = 7$, 17.9% vs 2% population prevalence)¹⁷. Previous studies have also reported increased psoriasis rates in AGEP patients (3–7%)⁵, though our cohort showed a more pronounced association. This raises the possibility of misclassified generalized pustular psoriasis (GPP); however, all our cases met EuroSCAR criteria, had identifiable drug triggers, showed eosinophils and spongiosis, and lacked arthritis or prior pustular psoriasis, supporting an AGEP diagnosis. We also considered the possibility of AGEP occurring in patients with established psoriasis—while psoriasis does not exclude AGEP, especially in the context of drug exposure, the clinical features, drug histories, and histology in our seven psoriasis patients favored AGEP over a pustular flare. This aligns with literature suggesting AGEP can arise independently in psoriatic patients.

In our study, a triggering factor was identified in 43 out of 51 cases (84.3%), with drugs being the trigger in 42 cases. Amoxicillin-clavulanate was the most frequently identified drug, involved in 8 cases (19%). This confirms the strong association of AGEP with antibiotic use ($n = 17$, 40%) in our study, as reported in the literature.^{8,11,16} Other drug classes associated with AGEP included antihypertensives, antiepileptics, and antimalarials. One patient developed AGEP after contracting COVID-19. The literature reported about 30 cases related to COVID-19, of which 26 were associated with drug intake (mostly hydroxychloroquine).¹⁸ In our patient, a history of flurbiprofen intake was

1 reported 7 days before AGEP development, and subsequently a diagnosis of COVID-19 was
2 performed, highlighting the need for a thorough history and consideration of alternative etiologies in
3 AGEP diagnosis.¹⁹

4 The mean latency from drug intake to the development of the skin condition was 10.7 days (range 5-50
5 days). Although AGEP is often said to have a relatively short latency, often less than 48 hours,
6 literature reports a variable range from 0 days to more than 30 days, which aligns with our cohort
7 data.¹⁶ Additionally a different time to onset has been described with different drugs.^{20 18}

8 Interestingly, patients with an EuroSCAR score greater than 9.5 had higher LDH levels, averaging
9 309.5 compared to 174.2 in patients with EuroSCAR < 9.5, a statistically significant difference in the
10 multivariate analysis. LDH, an enzyme involved in anaerobic metabolism, is released into the blood by
11 damaged or necrotic cells during inflammation, including the skin. This is the first time LDH levels
12 have been correlated with AGEP EuroSCAR score. The significant correlation suggests the potential
13 clinical utility of this marker in assessing AGEP, as it has been previously described for toxic
14 epidermal necrolysis.²¹ However, no specific assessments of cutaneous isoenzymes (LDH4 and 5)²¹
15 was performed in the current study.

16 A statistically significant association was also found between an EuroSCAR score > 9.5 and decreased
17 creatinine levels and higher eGFR in the univariate analysis. Although this seems paradoxical, closer
18 examination of the patients revealed that those with EuroSCAR > 9.5 had a mean age of 43.6 years,
19 18.5 years younger than the study average, and 22.8 years younger than patients with EuroSCAR < 9.5.
20 Therefore, we hypothesized that these results can be related to natural decline in renal function of about
21 1 mL/year starting at age 40 explains this difference. In addition to age, higher proportion of males
22 (who naturally have more muscle mass and higher baseline creatinine), pre-existing renal impairment,
23 medication effects, or other comorbidities might contribute to the paradoxical result of higher
24 creatinine levels in EuroSCAR less than 9.5 group.

Although not statistically significant, there was a trend towards higher EuroSCAR scores being associated with higher monocyte counts and itching. Itching was present in 100% of patients with EuroSCAR > 9.5 compared to 83.3% of patients with lower scores. Monocytosis was present, in 60% of patients with EuroSCAR > 9.5, compared to 16.7% in patients with lower scores. Taken together, these data indicate a more intense inflammatory and immune response in AGEP cases with increased EuroSCAR scores. Of note, monocytes are involved in the inflammatory response mediated by the release of Interleukin-36 (IL-36), a key cytokine in pustular reactions like AGEP and generalized pustular psoriasis (GPP).^{22,23} However, a diagnosis of AGEP is favored by the presence of a causative drug and the absence of arthralgia or history of arthritis, history of psoriasis or psoriasiform lesions and history of pustular disease.²⁴ In this setting, emerging therapies in GPP such as spesolimab, targeting IL-36 receptor, could be considered as a candidate for treating AGEP, especially for severe or steroid-refractory AGEP.²⁵ Regarding genetic findings, IL36RN gene (codifying IL-36 receptor antagonist) mutations are significantly associated with GPP but are rarely identified in AGEP. This rarity might indicate distinct genetic backgrounds, but the shared inflammatory mechanisms suggest some overlap, potentially explaining clinical similarities.²⁶⁻²⁹

Our histological findings were consistent with previous studies by the EuroSCAR and RegiSCAR groups, which analyzed 102 cases, with some differences. In our cohort, the main histopathological findings were: (i) spongiotic pustules (n = 43, 84.3%); (ii) eosinophilia (n = 42, 82.3%); (iii) neutrophilic exocytosis (n = 38, 74.5%); (iv) spongiosis (n = 37, 72.5%); and (v) dermal neutrophils (n = 37, 72.5%). Rare findings previously reported as frequent in the EuroSCAR-RegiSCAR study, like keratinocyte necrosis, were found in 5 cases (9.8%) compared to 68 (67%) and parakeratosis in 10 cases (19.6%) compared to 63 cases (62%).¹⁶ The rarity of keratinocyte necrosis and parakeratosis in our findings differs from previous AGEP studies, potentially due to variations in biopsy timing, case severity, or patient population. Early-stage biopsies or prior treatments (e.g., corticosteroids) may have

1 minimized these features. Alternatively, differences in diagnostic thresholds, histological techniques, or
2 immune response mechanisms could explain the discrepancy, warranting further investigation into
3 these factors.

4 In our patient cohort, skin biopsy, combined with clinical evaluation and history, allowed for a
5 definitive diagnosis in all patients. Confirmatory tests like patch tests and lymphocyte transformation
6 tests (LTT) were deemed unnecessary but could be considered in atypical clinical and historical cases
7 where histological examination is not definitive. The EuroSCAR scoring system was effective in our
8 cohort, with most patients (38 out of 39) achieving a definitive diagnosis and one patient having a
9 probable diagnosis (EuroSCAR 6).

10 As previously highlighted, AGEP mortality is extremely low, with no death in our study, supporting
11 findings from a large cohort of 340 AGEP patients in the US.⁸

12 The average time to resolution of the skin condition was 33.3 days (range 5 to 180 days), longer than
13 reported in the literature, where recovery is typically within a couple of weeks.⁸ This could be
14 explained by the timing of post-hospitalization follow-up visits. Although there are no standardized
15 guidelines for AGEP treatment, it is established that immediate cessation of the causative drug is key to
16 resolving the condition, possibly combined with systemic and/or topical corticosteroids and
17 antihistamines to speed up skin recovery and treat associated symptoms, particularly itching.³⁰ Potent
18 topical steroids and systemic steroids are also suggested as medical treatment by an European expert
19 consensus for the diagnosis and management of AGEP.³⁰ In our cohort, all patients discontinued the
20 suspected causative drug when present and underwent systemic and/or topical steroid therapy.

21 While this study provides valuable insights, it is limited by its retrospective nature, the cohort restricted
22 to Caucasians, and the absence of re-challenge tests to definitively identify causative agents. Future
23 studies should focus on prospective data collection and the inclusion of more diverse populations to
24 validate these findings. In particular, LDH should be further investigated, also in relation to systemic

involvement, together with recently validated EuroSCAR criteria.³¹ Additionally, research into the pathophysiological mechanisms underlying AGEP could uncover new therapeutic targets and improve management strategies.

Conclusions

Our study on AGEP currently represents one of the largest case series collected at a European level in recent years. Our study is the first to highlight the association of elevated LDH levels and fever in patients with a high EuroSCAR score (>9.5). The presence of spongiform pustules, eosinophils, neutrophilic exocytosis, and spongiosis were particularly frequent histopathological findings in our cohort, while other parameters previously reported as frequent, such as keratinocyte necrosis, were much rarer. Furthermore, a longer healing time was observed, likely due to the follow-up criteria. Ultimately, further research is necessary to clarify the immunopathological basis of AGEP and to develop standardized treatment guidelines. However, our study certainly provides new perspectives on systemic implications and new data regarding the histopathological characterization of AGEP.

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Figure legend

Figure 1. (a) Non-follicular pustules arising on large areas of oedematous erythema, involving mainly inguinal folds and corresponding **(b)** histopathology (hematoxylin-eosin stain, 100X magnification) highlighting non-follicular pustule (arrow) and intraepidermal pustule (asterisk).

Table 1. Baseline characteristics

	Total AGEF patients (n = 51)
Demographic data	
Age, mean $\pm$ SD (range)	61.8 $\pm$ 18.6 (1-93)
Females, n (%)	27 (52.9)
Males, n (%)	23 (47.1)
Comorbidities	
Cardiovascular diseases	21 (41.2)
Hematologic malignancies	5 (9.8)
Solid tumors	5 (9.8)
Psoriasis	3 (5.8)
Culprit drug, n (%)	43 (84.3)
Antimicrobials	
- Amoxicillin	8
- Fluoroquinolones	4
- Carbapenems (mero/ertapenem)	2
- Ampicillin	1

- Vancomicine	1
- Clarythromicin	1
- Oxacillin	1
Others	1
- Hydroxychloroquine	
- Allopurinol	3
- Coxib (celecoxib ed etoricoxib)	2
- Famciclovir	2
- Lamotrigine	2
- Metronidazole	1
- Ramipril	1
- Irbesartan	1
- Teriparatide	1
- Iron	1
- Ibandronate	1
- Pembrolizumab	1
- Eltrombopag	1
- Brotizolam	1
- Iomeron230 contrast agent	1
- Terbinafine	1
- Supplements	2
- Covid-19/flurbiprofen	1
	1
Latency of cutaneous symptoms, mean+/- SD (range)	10.7± 11.7 days (0-50)
AGEP duration, mean ± SD (range)	33.3 ± 4.9 days (5-180)
Mortality	0 (0)
RegiSCAR, mean+/- SD (range)	9.5 ± 1.4 (6-11)
Body surface area (BSA) BSA, mean+/- SD (range)	33.7 ± 24.1 (5-95)
Skin involvement, n (%)	
Trunk	36 (70.6)
Upper limbs	30 (58.8)
Lower limbs	31 (60.8)
Head-neck	19 (37.2)
Mucous membrane	3 (5.9)
Symptoms, n (%)	
Fever	17 (33.3)
Itch	36 (70.6)
Treatment, n (%)	
Systemic	
Corticosteroids	11 (28)
Antihistamines	2 (5.1)
Corticosteroids + antihistamines	19 (48.7)

Topical	
Corticosteroids	25 (64.1)
Emollients	1 (2.5)
	Subset of hospitalized patients (N=39)
Length of hospitalization, mean $\pm$ SD (range)*	14.5 $\pm$ 11.8 days (1-60)
Systemic involvement, n (%)*	
Liver	3 (7.7)
Kidneys	5 (12.8)
Blood tests, mean$\pm$ SD (range)*	
AST (aspartate aminotransferase) U/L	34 $\pm$ 53 (7-268)
ALT (alanine transaminase) U/L	39 $\pm$ 58 (10-248)
GGT (gamma-glutamyl transferase) U/L	72 $\pm$ 69 (7-221)
ALP (alkaline phosphatase) IU/L	113 $\pm$ 56 (45-257)
Calcium mg/dL	8.2 $\pm$ 2 (0.65-10.5)
Creatinine mg/dL	1.16 $\pm$ 1 (0.29-5.05)
eGFR (estimated Glomerular Filtration Rate) mL/min	75.7 $\pm$ 35.9 (8-143)
Urea mg/dL	57 $\pm$ 48 (19-202)
LDH (lactate dehydrogenase) U/L	250 $\pm$ 73 (148-392)
WBC (white blood cell) count $\times 10^3/\mu\text{L}$	16.2 $\pm$ 10.5 (4.27-53.6)
ESR (Erythrocyte sedimentation rate) mm/h	26 $\pm$ 26 (2-78)
CRP (C-reactive protein) mg/dL	5.4 $\pm$ 7.5 (0.1-34.65)

*accounted for 39 patients with blood tests available

Table 2. Histopathologic features

Histology	Frequency, n (%)
Acantosis	29 (56.8)
Spongiform and/or subcorneal pustules	43 (84.3)
Spongiosis	37 (72.5)
Exocytosis of neutrophils	38 (74.5)
Keratinocyte necrosis	5 (9.8)
Lymphocytes	33 (64.7)
Neutrophils in dermis	37 (72.5)
Eosinophils	42 (82.3)
Papillary dermis oedema	23 (45.1)
Superficial and interface infiltrates	21 (41.1)
Munro abscesses	31 (60.7)
Hyperkeratosis	18 (35.3)
Parakeratosis	10 (19.6)
Suprapapillary thinning	2 (3.9)
Vacuolar interface changes	9 (17.6)
Eosinophils in dermis	25 (49)
Interface dermatitis	3 (5.8)
Follicular pustules	5 (9.8)

Table 3. Univariate analysis highlighting correlations of clinical and laboratory parameters with EuroSCAR in 39 patients with blood tests available

		EuroSCAR score		Total	P-value
		EuroSCAR < 9.5 N=18	EuroSCAR > 9.5 N=21	Total N=39	p-value
Gender, n (%)	males	10 (55.6)	8 (38.1)	18 (46.2)	0.276
	females	8 (44.4)	13 (61.9)	21 (53.8)	
Age, mean $\pm$ SD (range)		62.5 $\pm$ 13.2 (38-85)	58.2 $\pm$ 23.7 (1-86)	60.3 $\pm$ 19.5 (1-86)	0.502
Ethnicity, n (%)	Caucasians	17 (94.4)	19 (90.5)	36 (92.3)	1
Comorbidities, n (%)		14 (77.8)	19 (90.5)	33 (84.6)	0.387
Liver involvement, n (%)		1 (5.6)	2 (9.5)	3 (7.7)	0.679
Kidney involvement, n (%)		3 (16.7)	2 (9.5)	5 (12.8)	0.634
History of psoriasis, n (%)		2 (11.1)	5 (23.8)	7 (17.9)	0.418
History of hematologic malignancies, n (%)		2 (11.1)	3 (14.3)	5 (12.8)	1
History of solid malignancies, n (%)		2 (11.1)	3 (14.3)	5 (12.8)	1
History of cardiovascular diseases, n (%)		11 (61.1)	10 (47.6)	21 (53.8)	0.399
More than 3 drugs, n (%)		10 (58.8)	7 (36.8)	17 (47.2)	0.187
Culprit drug antibiotic, n (%)		5 (27.8)	8 (38.1)	13 (33.3)	0.496
Culprit drug antimalarial, n (%)		1 (5.6)	2 (9.5)	3 (7.7)	1
Culprit drug xanthine oxidase inhibitors, n (%)		1 (5.6)	1 (4.8)	2 (5.1)	1
Culprit drug non-steroidal anti-inflammatory drugs, n (%)		2 (11.1)	0 (0)	2 (5.1)	0.206
BSA 11-30%, n (%)		5 (83.3)	2 (100)	7 (87.5)	1
BSA > 30%, n (%)		12 (70.6)	19 (90.5)	31 (81.6)	0.207
Head neck, n (%)		6 (35.3)	13 (61.9)	19 (50)	0.103
Trunk, n (%)		15 (88.2)	21 (100)	36 (94.7)	0.193
Upper limbs, n (%)		13 (76.5)	17 (81)	30 (78.9)	1
Lower limbs, n (%)		13 (76.5)	18 (85.7)	31 (81.6)	0.678
Mucosae, n (%)		3 (16.7)	0 (0)	3 (7.9)	0.081
Systemic infection associated, n (%)		3 (16.7)	4 (19)	7 (17.9)	1
Itch		15 (83.3)	21 (100)	36 (92.3)	0.089
Fever		4 (22.2)	13 (61.9)	17 (43.6)	0.023*
Latency of cutaneous symptoms, mean $\pm$ SD (range)		14.6 $\pm$ 14.7 (1-50)	6.8 $\pm$ 7.3 (1-32)	29	0.076
WBC count mean $\times 10^3/\mu\text{L} \pm \text{SD}$ (range)		17.7 $\pm$ 18.1 (4.27-53.8)	15.7 $\pm$ 7.8 (6.6-29.8)	16.2 $\pm$ 10.5 (4.27-53.6)	0.687
- Monocyte, count mean $\times 10^3/\mu\text{L} \pm \text{SD}$ (range)		0.67 $\pm$ 0.2 (2.39-15.47)	1.23 $\pm$ 0.9 (0.18-3.48)	1.1 $\pm$ 0.8 (0.18-15.47)	0.128
-Neutrophils, count mean $\times 10^3/\mu\text{L} \pm \text{SD}$ (range)		8.6 $\pm$ 5 (2.4-15.5)	11.7 $\pm$ 6.7 (3.3-23)	11 $\pm$ 6.4 (2.4-23.1)	0.252

-Eosinophils, count mean $\times 10^3/\mu\text{L} \pm \text{SD}$ (range)	0.3 $\pm$ 0.4 (0-1.1)	0.4 $\pm$ 0.5 (0-1.56)	0.4 $\pm$ 0.4 (0-1.56)	0.687
AST, U/L mean $\pm \text{SD}$ (range)	27.1 $\pm$ 12.7 (14-49)	37 $\pm$ 61.6 (7-268)	34 $\pm$ 53 (7-268)	0.704
ALT, U/L mean $\pm \text{SD}$ (range)	51.5 $\pm$ 71.4 (11-212)	34.6 $\pm$ 51.1 (8-248)	39 $\pm$ 58 (10-248)	0.518
GGT, U/L mean $\pm \text{SD}$ (range)	119.2 $\pm$ 61.2 (54-202)	56.8 $\pm$ 66.3 (7-221)	72 $\pm$ 69 (7-221)	0.120
ALP, IU/L mean $\pm \text{SD}$ (range)	126 $\pm$ 24 (109-143)	110.1 $\pm$ 61.8 (45-257)	113 $\pm$ 56 (45-257)	0.736
calcium, mg/dL mean $\pm \text{SD}$ (range)	7.45 $\pm$ 3.4 (0.65-9.9)	8.5 $\pm$ 0.9 (6.86-10.5)	8.2 $\pm$ 2 (0.65-10.5)	0.275
LDH, U/L mean $\pm \text{SD}$ (range)	174.2 $\pm$ 42.6 (148-238)	272.8 $\pm$ 65 (150-392)	250 $\pm$ 73 (148-392)	0.013*
CRP, mg/dL mean $\pm \text{SD}$ (range)	8.4 $\pm$ 14.1 (0.1-34.6)	4.4 $\pm$ 3.6 (0.1-11.2)	5.4 $\pm$ 7.5 (0.1-34.6)	0.268
urea, mg/dL mean $\pm \text{SD}$ (range)	89 $\pm$ 71.7 (34-202)	47.4 $\pm$ 35.4 (19-168)	57 $\pm$ 48 (19-202)	0.065
Creatinine, mg/dL mean $\pm \text{SD}$ (range)	2.08 $\pm$ 1.7 (0.79-5.05)	0.9 $\pm$ 0.6 (0.2-2.78)	1.16 $\pm$ 1 (0.2-5.05)	0.021*
eGFR, mL/min mean $\pm \text{SD}$ (range)	45.8 $\pm$ 33.4 (8-95)	84.5 $\pm$ 32.4 (32-143)	75.7 $\pm$ 35.9 (8-143)	0.030*
Length of hospitalization, mean $\pm \text{SD}$ (range)	10.6 $\pm$ 5.6 (5-20)	15.6 $\pm$ 12.9 (0-60)	14.5 $\pm$ 11.8 days (1-60)	0.409
AGEP duration, days mean $\pm \text{SD}$ (range)	48.4 $\pm$ 59.8 (5-180)	21.1 $\pm$ 19.5 (6-90)	33.3 $\pm$ 4.9 (5-180)	0.096

1

2 BSA: Body Surface Area; WBC: White Blood Cell; AST: Aspartate Aminotransferase; ALT: Alanine
3 Aminotransferase; GGT: Gamma-Glutamyl Transferase; ALP: Alkaline Phosphatase; LDH: Lactate
4 Dehydrogenase; CRP: C-Reactive Protein; eGFR: Estimated Glomerular Filtration Rate; AGEF: Acute
5 Generalized Exanthematous Pustulosis

6

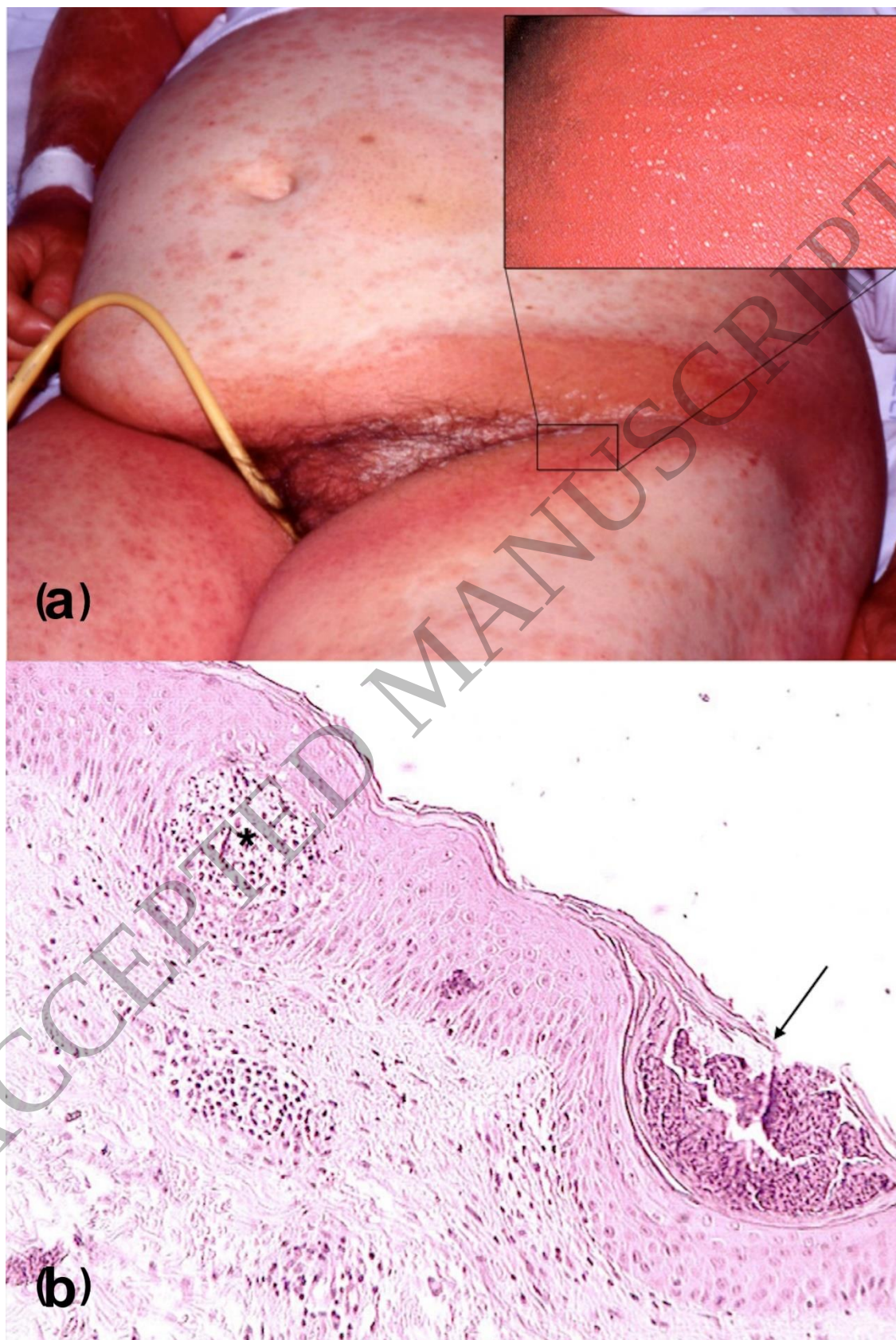


Figure 1
169x252 mm (x DPI)