

## ORIGINAL ARTICLE

# Palmoplantar pustulosis and acrodermatitis continua of Hallopeau: demographic and clinical comparative study in a large multicentre cohort

F. Assan,<sup>1</sup>  B. Husson,<sup>1</sup>  S. Hegazy,<sup>2</sup> J. Seneschal,<sup>3</sup>  F. Aubin,<sup>4</sup> E. Mahé,<sup>5</sup>  D. Jullien,<sup>6</sup>   
 E. Sbidian,<sup>7</sup>  M. D'Incan,<sup>8</sup> C. Conrad,<sup>9</sup>  E. Brenaut,<sup>10</sup>  C. Girard,<sup>11</sup> M.A. Richard,<sup>12</sup>   
 H. Bachelez,<sup>13,14,15</sup> M. Viguier,<sup>1,\*</sup> “Groupe de Recherche sur le Psoriasis” de la Société Française de Dermatologie

<sup>1</sup>Dermatology Department, Hôpital Robert-Debré, Reims, France

<sup>2</sup>Dermatology Department, Hôpital Larrey, Toulouse, France

<sup>3</sup>Dermatology Department, National Reference Center for Rare Skin Diseases, Hôpital Saint-André, Bordeaux, France

<sup>4</sup>Dermatology Department and Inserm 1098, Centre Hospitalo-Universitaire (CHU), Besançon, France

<sup>5</sup>Dermatology Department, Centre Hospitalier (CH), Argenteuil, France

<sup>6</sup>Clinical Immunology Department, CH Lyon-Sud, Lyon, France

<sup>7</sup>Dermatology Department, Hôpital Henri-Mondor, Créteil, France

<sup>8</sup>Dermatology Department, CHU Estaing, Clermont-Ferrand, France

<sup>9</sup>Dermatology Department, Lausanne University Hospital, CHUV, Lausanne, Switzerland

<sup>10</sup>Dermatology Department, CHU, Brest, France

<sup>11</sup>Dermatology Department, CHU Lapeyronie, Montpellier, France

<sup>12</sup>Dermatology Department, CEReSS-EA 3279, Research Center in Health Services and Quality of Life Aix Marseille University, University Hospital Timone, Assistance Publique Hôpitaux de Marseille, Marseille, France

<sup>13</sup>Université de Paris, Paris, France

<sup>14</sup>Dermatology Department, Assistance Publique-Hôpitaux de Paris, Hôpital Saint-Louis, Paris, France

<sup>15</sup>Laboratory of Genetics of Skin Diseases, INSERM UMR1163, Institut Imagine, Necker Hospital, Paris, France

\*Correspondence: M. Viguier. E-mail: mviguier@chu-reims.fr

## Abstract

**Background** Acral pustular disease within the pustular psoriasis/psoriasis-like spectrum mainly includes palmoplantar pustulosis (PPP) and acrodermatitis continua of Hallopeau (ACH). Scarce data argue for a distinction between these two entities, but no study has compared the clinical and epidemiologic characteristics of ACH and PPP.

**Objectives** We aimed to perform a comparative description of the epidemiological and clinical characteristics of PPP and ACH in a multicentre retrospective cohort.

**Methods** In this multicentre national retrospective cohort study, we compared the epidemiological characteristics, comorbidities and psoriasis characteristics of patients with PPP and ACH.

**Results** A total of 234 patients were included: 203 (87%) with PPP, 18 (8%) with ACH and 13 (6%) with both, according to 2017 ERASPEN criteria. As compared with ACH, PPP was associated with female sex, smoking activity and higher median BMI ( $P = 0.01$ ,  $P = 0.02$  and  $P = 0.05$  respectively). A family background of psoriasis was more frequent in PPP than ACH. Age of onset of palmoplantar disease was similar between PPP and ACH patients, median age 44 and 48 years respectively. Peripheral joint inflammatory involvement was the only rheumatic disease associated with ACH. The association with another psoriasis type was similar in PPP and ACH (57.6% and 61.1% respectively).

**Conclusion** Our study confirms in a large PPP cohort the predominance of females and a high prevalence of smoking and elevated body mass index but also shows an association of these features in PPP as compared with ACH. In addition, it highlights peripheral arthritis as the only arthritis endotype associated with ACH. Increased knowledge of the immunogenetic backgrounds underlying these two entities is warranted to better stratify pustular psoriasis or psoriasis-like entities for precision medicine.

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## Conflict of interest

None.

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None.

## Introduction

Acral pustular psoriasis is a rare and disabling variant of psoriasis, associated in the literature with middle-aged women and smoking.<sup>1,2</sup> In 2017, the European Rare and Severe Psoriasis Expert Network (ERASPEN) differentiated two clinical forms: palmoplantar pustulosis (PPP) and acrodermatitis continua of Hallopeau (ACH).<sup>3</sup>

Some evidence argues for a specific transcriptomic and genetic pattern of PPP, distinct from psoriasis vulgaris (PV) or generalized pustular psoriasis (GPP),<sup>4,5</sup> but the clinical and pathophysiological characteristics of ACH and PPP have not been compared. In a recent study reporting the efficacy of biological therapy in acral pustular psoriasis, we showed that ACH patients had a specific response profile as compared with PPP patients, with a higher proportion of complete clearance with adalimumab or etanercept.<sup>6</sup> These data would imply that these diseases are true distinct entities.

Here we compared the epidemiological and clinical characteristics of PPP and ACH in a multicentre retrospective cohort.

## Patients and methods

### Study design and setting

We analysed epidemiological and clinical data for a multicentric retrospective cohort of PPP and ACH patients followed by expert dermatologists registered as members of the 'Groupe de Recherche sur le Psoriasis' of the French Society of Dermatology. We performed a search of the literature in PubMed using the keywords "palmoplantar AND pustulosis", "palmoplantar AND pustulosis AND psoriasis". Among the 633 published studies, only cohort studies ( $n > 15$ ) published in English were selected. Of note, studies included for comparison with our PPP cohort had to exclude or mention the proportion of patients presenting an eventual associated ACH, based on the ERASPEN criteria.<sup>3</sup> However, only one cohort study assessing the detailed clinical characteristics of ACH was found.

### Participants and eligibility criteria

Patients were included if they (1) had a diagnosis of PPP and/or ACH by a certified dermatologist and (2) were followed by one of the study investigators for a minimum of 12 weeks after initiating at least one topical or one systemic treatment for PPP and/or ACH between January 2014 and December 2016. Some

patients of the present cohort ( $n = 92$ ) were included in a previous study of our group.<sup>6</sup> Patients with drug-induced pustular psoriasis were excluded, mainly those with tumour necrosis factor inhibitor-induced paradoxical PPP.

### Data collection and definitions

The following data were collected at inclusion: demographic data (sex, smoking status, alcohol consumption), clinical data including subtype of acral pustular psoriasis (PPP, ACH and overlap), age at disease onset, comorbidities (dyslipidaemia, hypertension, diabetes, hypo- or hyperthyroidism, body mass index), association with other types of psoriasis, including psoriatic arthritis, indicators of severity of associated plaque psoriasis/psoriasis vulgaris (PV) (Psoriasis Area Severity Index [PASI] and body surface area [BSA]).

Acral pustular psoriasis subtype definitions followed the European consensus<sup>3</sup>: ACH was defined by primary, persistent ( $>3$  months), sterile, macroscopically visible pustules affecting the nail apparatus and PPP by primary, persistent ( $>3$  months), sterile, macroscopically visible pustules on palms and/or soles. Overlap forms associated characteristics of both ACH and PPP. Synovitis, Acne, Pustulosis, Hyperostosis, and Osteitis (SAPHO) syndrome was defined according to the inclusion and exclusion criteria formulated by Benhamou *et al.*<sup>7</sup> Overweight and obesity were defined by body mass index (BMI)  $\geq 25$  and  $30 \text{ kg/m}^2$  respectively.

### Statistical analysis

Data are presented as median (interquartile range [IQR]) or number (%). We used Fisher's exact test and Mann-Whitney test to compare as appropriate categorical and unpaired non-normally distributed quantitative data respectively. Two-tailed  $P \leq 0.05$  was considered statistically significant in exploratory analysis. Multiple testing was corrected by two-stage linear step-up procedure of Benjamini, Krieger and Yekutieli (Q: 5%); after correction p-values less than 0.0087 were considered as 'discoveries'. Analyses were performed with GraphPad Prism version 8. Patients with the overlap subtype of acral pustular psoriasis were excluded from the statistical analysis in order to compare only ACH and PPP phenotypes.

### Ethical statements

The research was conducted in compliance with the Helsinki Declaration. According to French law, this study was declared to

the Commission Nationale de l'Informatique et des Libertés (CNIL, declaration no. 2206749, 09/13/2018).

## Results

Patient characteristics are summarized in Table 1. A total of 234 patients were included: 160 (68%) were females. PPP was the most frequent form (87%,  $n = 203$ ) as compared with ACH (8%,  $n = 18$ ) and the overlap form (6%,  $n = 13$ ).

### Comparison between ACH and PPP patients

The proportion of females was significantly higher for PPP than ACH patients (71.4% vs. 38.8%,  $P = 0.007$ ; Table 1). Overall, 20.2% PPP patients had a family history of psoriasis (all combined), with none reported in the ACH group. Age of onset of palmoplantar disease was similar between the PPP and ACH groups (median age 44 [IQR 32–52] vs. 48 [30–6] years).

In addition, the prevalence of active smoking was significantly higher in PPP than ACH (60.6% vs. 44.4%,  $P = 0.04$ ). In addition, the median BMI was higher in PPP group (25.2 [IQR 22.4–31.2]

vs. 23.6 [21.0–25.3]  $\text{kg/m}^2$ ,  $P = 0.05$ ). In line with these data, the proportion of overweight and obese patients was higher in PPP than ACH (39.4% vs. 27.8% and 20.7% vs. 5.6%, data not shown). The prevalence of cardiometabolic comorbidities (dyslipidaemia, hypertension, diabetes) did not differ between the groups.

The groups did not differ in prevalence of rheumatological inflammatory disease, including SAPHO syndrome. However, peripheral arthritis was the only inflammatory rheumatic disease associated with ACH than PPP (27.8% vs. 6.4%). The association with another psoriasis type was similar between the PPP and ACH groups (57.6% and 61.1%). When another type of psoriasis was associated, ACH and/or PPP onset occurred in most cases before the onset of any psoriasis subtype (86.7% and 88.9% in, respectively, PPP and ACH). PV was the most frequent associated type of psoriasis in both cases, ahead of nail psoriasis. Nail involvement and flexural psoriasis were higher in overlap patients, 61.5% and 15.4%, respectively, than the other groups. GPP prevalence was higher in ACH than PPP, but the number of GPP patients in each group was too low for analysis.

**Table 1** Clinical characteristics of patients with acral pustular psoriasis and comparison of PPP and ACH

	Total ( $n = 234$ )	PPP ( $n = 203$ )	ACH ( $n = 18$ )	Overlap ( $n = 13$ )	PPP vs. ACH $P^*$
Female, $n$ (%)	160 (68.3)	145 (71.4)	7 (38.8)	8 (61.5)	<b>0.007</b>
Psoriasis family history, $n$ (%)	44 (18.8)	41 (20.2)	0 (0)	3 (23.1)	<b>0.03†</b>
Age at onset, median (IQR)	44 (31–53)	44 (32–52)	48 (30–65)	42 (30–51)	0.27
Smoking, $n$ (%)	166 (70.9)	149 (73.4)	8 (44.4)	9 (69.2)	<b>0.004</b>
Current, $n$ (%)	134 (57.3)	123 (60.6)	7 (38.9)	4 (30.8)	
Former, $n$ (%)	21 (9.0)	16 (7.9)	1 (5.5)	4 (30.8)	
Excessive alcohol consumption, $n$ (%)	26 (11.1)	18 (8.9)	4 (22.2)	4 (30.8)	0.12
BMI, median (IQR)	25 (22.2–29.6)	25.2 (22.4–31.2)	23.6 (21.0–25.3)	22 (18.6–28.4)	<b>0.05†</b>
Dyslipidaemia, $n$ (%)	40 (17.1)	38 (18.7)	1 (5.6)	1 (7.7)	0.21
Hypertension, $n$ (%)	46 (19.7)	41 (20.2)	4 (22.2)	1 (7.7)	0.77
Diabetes, $n$ (%)	23 (9.8)	19 (9.4)	4 (22.2)	0 (0)	0.10
Hypo/hyperthyroidism, $n$ (%)	15 (6.4)	14 (6.9)	0 (0)	1 (7.7)	0.61
APP as first manifestation of psoriasis, $n$ (%)	204 (87.2)	176 (86.7)	16 (88.9)	12 (92.3)	1
Association with psoriasis, $n$ (%)	138 (59.0)	117 (57.6)	11 (61.1)	10 (76.9)	0.81
Psoriasis vulgaris	100 (42.7)	87 (42.9)	6 (33.3)	7 (53.4)	
Psoriasis guttate	13 (5.6)	11 (5.4)	2 (11.1)	0 (0)	
Flexural psoriasis	14 (6.0)	11 (5.4)	1 (5.6)	2 (15.4)	
Nail psoriasis	63 (26.9)	50 (24.6)	5 (27.8)	8 (61.5)	
GPP	3 (1.3)	1 (0.5)	2 (11.1)	0 (0)	
Arthritis, $n$ (%)	53 (22.6)	45 (22.2)	5 (27.8)	3 (23.1)	0.57
Axial	10 (4.3)	10 (4.9)	0 (0)	0	
Peripheral	20 (8.5)	13 (6.4)	5 (27.8)	2 (15.4)	
Overlap	20 (8.5)	19 (9.4)	0 (0)	1 (7.7)	
SAPHO	13 (5.6)	13 (6.4)	0 (0)	0 (0)	

ACH, acrodermatitis continua of Hallopeau; APP, acral pustular psoriasis; BMI, body mass index; BSA, body surface area; GPP, generalized pustular psoriasis; IQR, interquartile range; PASI, Psoriasis Activity Skin Index; PPP, palmoplantar pustulosis; PV, psoriasis vulgaris; SAPHO, Synovitis Acnea Hyperostosis and Osteitis; Overweight and obesity were defined with BMI > 25 and 30  $\text{kg/m}^2$  respectively.

$P$  values < 0.05 are indicated in bold.

\*Fisher's exact test for categorical variables and Mann–Whitney test for continuous variables.

†Statistically significant in exploratory analysis but not after multiple testing correction (Two-stage linear step-up procedure of Benjamini, Krieger and Yekutieli).

In case of associated PV, PASI and BSA were similar between groups (respectively, median 11.5 [IQR 8.3–14.8] vs. 6 [4.2–15.2]; and 5 [4.25–8.75] vs. 3 [1.5–10], data not shown).

### Comparison with the literature

We found four cohorts from three different studies in the literature reporting clinical characteristics of PPP; two were monocentric, and none had a study size larger than our cohort (Table 2).<sup>8–10</sup> The proportion of females ranged from 59% to 83%, with the median age at disease onset of 44.2 to 51.1 years, which agrees with our data. In our cohort, the respective rates of hypertension, current/former smokers and thyroid disease were comparable with the literature, but the prevalence of diabetes was slightly less in our study (12.1% to 15% vs. 9.8% in our cohort).

The 42.7% proportion of our patients with acral pustular disease showing an association with PV exceeded the highest prevalence rates from the literature, which ranged from 11% to 33%.<sup>8–10</sup> In the same way, the prevalence of arthritis was higher in our cohort than the literature (22.6% vs. 8.6% to 16.7% [8–10]). Several biases might account for these apparent discrepancies, especially the massive tertiary care centre recruitment in our study, which might affect patient profiles, including severity, as well as physician assessments.

For an international genotyping study of 863 patients with pustular psoriasis across different geographic areas, clinical data were not available in detail.<sup>4</sup> Recently, only one cohort study reported characteristics of 39 ACH patients<sup>11</sup> with the prevalence of smoking and associated inflammatory rheumatism and median BMI comparable to that in our study. However, female

**Table 2** Comparison of PPP clinical characteristics in the current study to previous series

	Benzian-Olsson <i>et al.</i> <sup>10</sup>		Kim <i>et al.</i> <sup>9</sup>	Huang <i>et al.</i> <sup>8</sup>	Current study
Series characteristics	Prospective multicentre	Prospective multicentre	Retrospective monocentre	Retrospective monocentre	Retrospective multicentre
Series country	United Kingdom	Northern Europe	Korea	Taiwan	France
Year of publication	2020	2020	2020	2020	
Distinction with ACH and/or PPP diagnosis based on 2017 ERASPEM criteria	Yes (ACH excluded)	Yes (ACH excluded)	No†	Yes	Yes
Total population	203	193	116	66	203
Age at onset, median (SD or range), years	48 (38–59)	45 (33–54)	51.1 (11.1)	44.2 (14.3)	44 (22)
Female, <i>n</i> (%)	160 (79)	161 (83)	69 (59.5)	39 (59.1)	145 (71)
Nail involvement, <i>n</i> (%)	65 (32)	64 (33)	63 (66.3)	31 (47.0)	50 (25)
Smoking, <i>n</i> (%)	178 (87.7)	160 (82.9)	NA	41 (62.1)	149 (74)
Family history, <i>n</i> (%)					
Pustular psoriasis	9 (4)	10 (11)	NA	NA	5 (2.5)
PV	65 (32)	33 (17)	NA	NA	31 (15)
Psoriasis all combined, <i>n</i> (%)	NA	NA	NA	1 (1.5)	41 (20)
Personal background, <i>n</i> (%)					
PV	66 (33)	22 (11)	17 (14.7)	14 (21.2)	87 (43)
Rheumatism involvement	20 (10)	17 (9)	10 (8.6)	11 (16.7)	45 (22)
GPP	NA	NA	NA	3 (4.5)	1 (0.5)
ACH	Exclusion criteria	Exclusion criteria	5 (7.9)†	5 (7.6)	0 (0)
Comorbidities, <i>n</i> (%)					
Hypertension	41 (20)	58 (30)	21 (18.1)	10 (15.2)	41 (20)
Diabetes	26 (13)	29 (15)	14 (12.1)	8 (12.1)	19 (9.3)
Hypo/hyperthyroidism	14 (7)	25 (13)	6 (5.2)	4 (6.1)	14 (6.9)
SAPHO	NA	NA	NA	1 (1.5)	13 (6)
Overweight	NA	NA	NA	NA	80 (39)
Obesity	60 (40)	51 (26)	NA	NA	42 (21)
Dyslipidaemia	NA	NA	NA	NA	38 (19)

ACH, acrodermatitis continua of Hallopeau; ERASPEM, European Rare and Severe Psoriasis Expert Network; GPP, generalized pustular psoriasis; NA, not available; PPP, palmoplantar pustulosis; PV, psoriasis vulgaris; SAPHO, Synovitis Acnea Palmoplantar pustulosis Hyperostosis and Osteitis; SD, standard deviation.

Overweight and obesity were defined as BMI > 25 and 30 kg/m<sup>2</sup> respectively.

†PPP diagnosis was not based on ERASPEM criteria, but ACH diagnosis was deduced from description of nail involvement on the study, as subungual pustulation.

prevalence, age at onset and associated psoriasis vulgaris were higher than in our cohort (56.4% vs. 38.8%, 54.4 vs. 48 years old and 46.2% vs. 33.3% respectively). Of note, 18% of these patients presented associated PPP. In addition, given the low number of ACH patients, comparative analyses of cohort studies should be considered with caution.

## Discussion

This is the first study comparing the epidemiological and clinical characteristics of PPP and ACH, defined according to 2017 ERAS-PEN criteria.<sup>3</sup> We show evidence of an overlap in 6% of our patients who fulfilled ERAS-PEN criteria for both entities. Otherwise, our study emphasizes that PPP and ACH are distinct clinical entities in most cases. In addition, we show that PPP is associated with smoking and with an elevated BMI, whereas arthritis, predominantly peripheral, seemed to predominantly affect patients with ACH.

In our study, peripheral arthritis was the only inflammatory rheumatic disease found in ACH. An association between enthesitis and nail psoriasis was previously reported: the prevalence of nail psoriasis was increased among patients presenting psoriatic arthritis,<sup>12</sup> but its severity was also associated with distal interphalangeal joint involvement and unremitting arthritis.<sup>13</sup> In fact, given the anatomical relation between nail root and distal interphalangeal joints, inflammation of this joint surrounds the nail matrix, thus leading to psoriatic nail disease by Koebner phenomenon.<sup>14</sup> A similar scenario could explain the association between ACH and peripheral rheumatism, by a peripheral tropism of inflammation. Of note, nail psoriasis prevalence was similar between ACH and PPP, which excludes it as a potential confounding factor.

We confirmed the association of environmental factors such as tobacco smoking with PPP, in accordance with the literature. Furthermore, less than 3% of our PPP group had a family history of PPP, as compared with 15% having a family history of PV. This finding highlights the importance of environmental factors in a given family background for PPP development. The Twelves *et al.* large cohort study, genotyping 863 patients with pustular psoriasis (251 GPP, 560 PPP, 28 ACH and 24 overlap), reported that PPP was the pustular psoriasis type most affected by smoking status, whereas the proportion of patients carrying *IL36RN* mutations was greater in GPP and ACH than PPP.<sup>4</sup> In our cohort, family history of psoriasis in ACH patients may have been underestimated because of the variable manifestation of psoriatic disease and the retrospective nature of the study. For example in the Kromer *et al.* study, 2% of patients had a family history of pustulosis and 23% a family history of PV.<sup>11</sup> In the Twelves *et al.* study, the proportion of ACH patients carrying *IL36RN* disease alleles was 18.2%.<sup>4</sup>

PPP severity was recently found associated with smoking status.<sup>10</sup> Despite no doubt about a genetic part in PPP, either complex or monogenic, the environment seems to play a major role

in its development and severity. Actually, several data argue for a direct role of pyrenes in the excretion of stress-induced cytokines in keratinocytes as a Koebner phenomenon.<sup>15,16</sup> Taken together, these data provide support for a role of tobacco smoke contaminants in both local palmar and systemic inflammation. Finally, a 2006 study showed a significant alleviation of PPP among patients who stopped smoking as compared with those who continued,<sup>17</sup> which raises the importance of a focus on smoking cessation in patients with PPP.

In the same way, elevated BMI tended to be associated with PPP. The impact of obesity on PV severity and in biological therapy resistance is well described,<sup>18–20</sup> but our study is the first to report in PPP. Given (i) the activation of the T helper 17 (Th17) cell pathway in obesity due to fatty acids and adiponectin,<sup>21–24</sup> (ii) the association of PPP with overweight, (iii) a reported efficiency of interleukin-17 (IL-17), IL-12/23 and IL-23 inhibitors<sup>6,25–27</sup> in PPP, the Th17 pathway could be involved in PPP development, as previously suggested.<sup>5,28,29</sup> Furthermore, recent data reported the efficacy of tumour necrosis factor inhibitors but with a higher proportion of complete response in ACH than PPP.<sup>6</sup> This differential pattern could be due to epidemiological cofounding factors such as smoking status and overweight, but we cannot exclude different immunological substrata between the two diseases, while no data are available for the ACH immunological pattern regarding for instance the activation of the IL-17 pathway.

Our study has some limitations, including its retrospective nature and the relatively small ACH cohort largely due to the extreme rarity of this latter pustular disease endotype,<sup>4</sup> which may impact statistical power. Moreover, PPP/ACH severity was not assessed in our cases by either PPPASI or PPPGA, as these scores are not validated yet in ACH, and as clinical scores are currently used/restrained for prospective clinical trials. Finally, one missing data of interest would be the differential phenotypes of PPP (i.e. vesicular vs. pustular forms). If the acrosyringium has been shown to be involved in the PPP vesicle formation,<sup>28</sup> mechanisms and triggers (i.e. pyrenes, systemic inflammation, mechanical stress, microorganisms) behind differential phenotypes evolution of PPP (vesicular or pustular) vs. ACH are still unclear. It would be of interest in larger scale and mechanistic studies to include this data for a better understanding of these diseases.

Despite these limitations, the robustness of our study assessing characteristics of PPP and ACH is reinforced by its multicentric nature, and by the use of recent ERAS-PEN consensus criteria. In addition, statistical analysis took into account the alpha risk inflation, thereby supporting the relevance of this set of data.

## Conclusions

Acral forms of pustular psoriasis are severe and disabling. Our study confirms the high prevalence of females and smoking in

PPP but also shows a specific association of these parameters in PPP as compared with ACH. Our study suggests that PPP and ACH might well be distinct diseases, despite some overlap. Likewise, they might not be as mutually different as for GPP and PV, and prospective phenotype-genotype and multiomics studies are warranted to better characterize the respective mechanistic scenario operating in each subgroup, opening the realistic perspective of a new pustular disease taxonomy. A better description of differential immunogenetic, epigenetic and environmental backgrounds underlying these two entities, in larger-scale studies, might help stratify these patients and precision management.

### Data availability statement

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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