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ORIGINAL ARTICLE

Characteristics and management of generalized pustular psoriasis (GPP): Experience from the Central and Eastern Europe (CEE) GPP Expert Network

P. Wolf[1] | R. Ceovic[2] | C. Conrad[3] | K. Falkensteiner[1] | T. Graier[1] | M. Kołt-Kamińska[4] | M. Marovt[5] | V. Mateeva[6] | J.-T. Maul[7,8] | A. A. Navarini[9] | A. C. Nicolescu[10] | G. Ratzinger[11] | L. Pavlovsky[12] | M. Sanzharovskaya[13] | A. Szegedi[14] | A. Reich[4]

[1]Department of Dermatology and Venereology, Medical University of Graz, Graz, Austria
[2]Department of Dermatology and Venereology, School of Medicine University of Zagreb, University Hospital Centre Zagreb, Zagreb, Croatia
[3]Department of Dermatology, Lausanne University Hospital, Lausanne, Switzerland
[4]Department of Dermatology, Institute of Medical Sciences, Medical College of Rzeszów University, Rzeszów, Poland
[5]Department of Dermatology, University Medical Centre Maribor, Maribor, Slovenia
[6]Department of Dermatology, Medical University of Sofia, Sofia, Bulgaria
[7]Department of Dermatology, University Hospital of Zürich, Zürich, Switzerland
[8]Faculty of Medicine, University of Zürich, Zürich, Switzerland
[9]Department of Dermatology, University Hospital of Basel, Basel, Switzerland
[10]Emergency Clinical Hospital Agrippa Ionescu, Bucharest, Romania
[11]Department of Dermatology, Venereology and Allergology, Medical University of Innsbruck, Innsbruck, Austria
[12]Division of Dermatology, Rabin Medical Center, Tel Aviv University, Tel Aviv, Israel
[13]Boehringer Ingelheim, Vienna, Austria
[14]Department of Dermatology, University of Debrecen, Debrecen, Hungary

Correspondence
P. Wolf, Department of Dermatology and Venereology, Medical University of Graz, Auenbruggerplatz 8, A-8036 Graz, Austria.
Email: peter.wolf@medunigraz.at

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Abstract

Background: Generalized pustular psoriasis (GPP) is a rare, inflammatory skin disease characterized by widespread eruption of sterile pustules with or without systemic symptoms.

Objectives: This study aimed to describe the demographics of patients with GPP in Central and Eastern Europe (CEE), present the clinical characteristics of individual GPP flares and explore the current treatment landscape.

Methods: Patient demographics were collected at the times of last observation and previous treatment. Characteristics of a patient's last (most recent) and most severe (from all documented episodes) flare were provided at clinician's discretion.

Results: Fifty-eight patients were recruited from 12 centres in nine CEE countries; median (range) age was 61 (16–92) years and 60.3% (35 out of 58) were female. The most common comorbidities were hypertension (43.1% [25 out of 58]) and hyperlipidaemia (32.8% [19 out of 58]). Thirty-four patients (58.6%) presented with concomitant plaque psoriasis before or during the course of GPP. Data from two separate flares were recorded in 26 individuals; in 32 patients, the most recent flare was

reported as the most severe. Over 90% of patients with a flare episode classified as most severe by clinicians were hospitalized, with >75% of these individuals having a Generalized Pustular Psoriasis Physician Global Assessment (GPPGA) total score of 3 or 4. Systemic symptoms were more common in patients with a GPPGA score of 3 or 4 but were also manifest in individuals with a GPPGA score ≤2. A significant correlation was observed between a combined systemic disease score of clinical and laboratory features and both GPPGA total score ($r = 0.385$, $p < 0.001$) and GPPGA pustulation subscore ($r = 0.305$, $p < 0.05$).

Conclusions: Considerable heterogeneity in the presentation of GPP flares was observed, both between patients and within-patient. All GPP flares were associated with a significant clinical burden, highlighting the unmet need for accurate and early diagnosis.

INTRODUCTION

Generalized pustular psoriasis (GPP) is a chronic, rare neutrophilic skin disease characterized by sudden episodes of widespread rash and eruption of primary, sterile, macroscopically visible pustules on non-acral skin.[1–3] GPP can occur with pre-existing plaque psoriasis, but has also been shown to occur independently and is recognized as a clinically distinct entity.[2,4] The clinical course of GPP is heterogeneous, with flare severity varying between individuals and even between separate episodes in the same patient.[2,3] GPP flares are frequently accompanied by systemic symptoms, including fever, malaise and leucocytosis,[3,4] and may lead to hospitalization and life-threatening complications.[5,6]

Global estimates of GPP prevalence vary considerably between countries, ranging from 1.76 to 124 patients per million persons.[7] GPP is associated with a significant clinical burden, including pain, fever and fatigue, and with several comorbidities that can significantly impact quality of life.[7–9] Additionally, patients with GPP often experience anxiety and depression.[10,11] In the absence of globally accepted guidance for the management of GPP flares or long-term treatment of disease,[9] immunomodulatory therapies including oral retinoids, cyclosporine and methotrexate are often given as first-line therapy.[12] However, their use is based on current treatments for plaque psoriasis, and there is limited evidence for GPP-specific efficacy of anti-psoriatic drugs, including biologics.[12]

To date, a number of biologic agents targeting cytokines in various pro-inflammatory pathways (tumour necrosis factor alpha, interleukin [IL]-17 and IL-23) have been approved for the treatment of GPP in selected countries (e.g. Japan and Thailand).[13–24] However, these approvals are based on limited evidence from small open-label clinical trials and case studies in Asian populations.[13–21,23] Biologic agents targeting the IL-36 pathway are also in development for the treatment of GPP, with the humanized anti-IL-36R monoclonal antibodies spesolimab and imsidolimab being evaluated in randomized controlled trials (RCTs).[25–28] Spesolimab was shown to be an effective treatment for GPP in Effisayil 1 (NCT03782792), the largest RCT to date to assess biologic use in patients experiencing a GPP flare.[25] Results from this study have led to the approval of spesolimab for the treatment of GPP flares in adults in the United States, Europe, Japan and China.[29–32]

There are significant challenges in understanding the epidemiology of GPP, due to the rarity and heterogeneity of the disease and to non-standardized study methods. The aims of this retrospective case-series study were to describe the demographics of patients with GPP in Central and Eastern Europe (CEE), to share experiences of the clinical characteristics of GPP flares and to explore the current treatment landscape in the CEE region.

MATERIALS AND METHODS

Study population

A retrospective case-series study evaluating demographic information for patients with GPP in CEE was conducted between March 2022 and December 2022 in 12 sites across nine CEE countries (Figure S1). Patients were eligible if they met GPP diagnosis criteria (as defined by the centre of excellence or the European Rare and Severe Psoriasis Expert Network [ERASPEN] criteria)[2] and had had follow-up or treatment within the past 10 years. Patients selected for potential inclusion were re-evaluated using ERASPEN criteria to confirm the GPP diagnosis.[2]

Data collection method

Information from medical records was extracted using a case report form (CRF) (Figure S2), collecting data on patient demographics at the most recent observation and past treatments. Clinical characteristics were provided for a patient's last (most recent) flare and most severe flare, which was designated at clinician's discretion from all documented episodes.

Data analysis

Analyses were performed on patient demographics at last observation, including data on concomitant diseases, GPP

history, duration of GPP, number of flares since diagnosis, number of flares requiring hospitalization or intensive care unit (ICU) admission and trigger factors. Clinical characteristics, including flare duration, hospitalization/ICU care required, Generalized Pustular Psoriasis Physician Global Assessment (GPPGA) total and component scores,[33,34] percentage of body surface area (BSA) affected, systemic inflammation symptoms and markers, were assessed for each flare episode. Information on treatments received for GPP, duration of treatment and time from treatment initiation to flare resolution was also collected; resolution was defined as total clearance of skin lesions with GPPGA pustulation and GPPGA scaling/crusting scores of 0.

Statistical methods

Descriptive statistics (including median, range, mean and standard deviation [SD]) were generated for all demographic data and clinical characteristics. Statistical comparison between patient groups was not appropriate given the cross-sectional nature of data collection.

Combined systemic disease score

To provide a quantitative measure of the severity of a patient's systemic symptoms, a combined systemic disease score (0–6) was assigned to each individual based on the presence of systemic inflammation symptoms and markers of inflammation during each flare. A cumulative score was derived by awarding one point for the presence of any the following: fever [>38°C], elevated C-reactive protein (CRP) levels (>5 mg/L), elevated leucocyte levels (>10,000 or >13,000 μL), hypocalcaemia (<2.1 mmol/L), hypoalbuminaemia (<35 g/L) and elevated transaminase levels (serum alanine transaminase level >35 or >45 U/L; serum aspartate transaminase level >35 or >40 U/L); the presentation of two cut-off levels for select laboratory parameters is due to the limits having been derived from the normal distribution of values collected at laboratories of different participating centers. Pearson correlation analysis was performed using data from all individual flares to determine the association between the combined systemic disease score and the GPPGA total score, GPPGA pustulation subscore and duration of flare.

RESULTS

Study population

Seventy-one patients were identified; of these, 58 were eligible and included in the analysis population from 12 sites in nine countries (Figure S2). Thirteen patients were excluded from further analysis due to not fulfilling ERASPEN criteria for GPP having experienced only one flare lasting <3 months ($n = 10$), the presence of plaque-type *psoriasis* cum *pustulatione* ($n = 2$) or acral disease manifestation ($n = 1$). Diagnosis was confirmed by skin biopsy in 80.4% (45 out of 56) patients, with data unavailable for two patients.

Demographics and clinical characteristics

Demographics data for all patients, and by sex and by presence of plaque psoriasis at any point during the disease course, are shown in Table 1. There was a slight predominance of female patients ($n = 35$; 60.3%) and the median (range) age was 61 (16–92) years (Table 1). Distribution of GPP cases by sex and age at GPP diagnosis, with cases of drug or infection flare triggers, is shown in Figure 1. The highest proportion of GPP diagnoses occurred between 61 and 70 years of age in both male and female patients (Figure 1). Trigger factors for GPP flares included infection (34.5% [20 out of 58]), such as infection with the SARS-CoV-2 virus (COVID-19), urinary tract infection or upper respiratory tract infection, and initiation or withdrawal of treatment (22.4% [13 out of 58]) including systemic steroids and antibiotics (Table 1). Seven patients presented with both drug and infection triggers, though these events may not have occurred simultaneously (Figure 1). Median (range) disease duration was 8 (0.25–51) years and the mean (SD) flare frequency was 0.98 (0.93) flares per year. There were no differences in median GPPGA total score for an individual's most severe flare between sexes or between those with and without a history of plaque psoriasis (Table 1). Flares were triggered by ceasing treatment with systemic steroids in two female patients, both of whom presented with concomitant plaque psoriasis (Table 1).

The most common comorbidities in the patient population were hypertension (43.1% [25 out of 58]) and hyperlipidaemia (32.8% [19 out of 58]; Table 1). Results were generally comparable in male and female participants, and between those with and without a history of plaque psoriasis. However, 54.3% (19 out of 35) of female patients and 65.2% (15 out of 23) of male patients presented with a history of plaque psoriasis. Data regarding genetic mutations associated with GPP were not available.

Patients with GPP and a history of other forms of psoriasis

Thirty-four out of 58 patients (58.6%) had concomitant plaque psoriasis at any point before or during the GPP disease course (Table 1). Other psoriasis variants characterized by location were more common in individuals with a history of plaque psoriasis compared with those without, including scalp psoriasis (35.3% [12 out of 34] vs. 4.2% [1 out of 24], $p = 0.005$), chronic nail psoriasis (29.4% [10 out of 34] vs. 4.2% [1 out of 24], $p = 0.016$), intertriginous psoriasis (26.5% [9 out of 34] vs. 12.5% [3 out of 24], $p = 0.196$) and palmoplantar pustulosis (14.7% [5 out of 34] vs. 8.3%

TABLE 1 Patient demographics and medical history.

Characteristic	All patients (*N* = 58)	Female (*n* = 35)	Male (*n* = 23)	GPP with plaque psoriasis (*n* = 34)	GPP without plaque psoriasis (*n* = 24)
Age, years, median (range)	61 (16–92)	58 (20–87)	62 (16–92)	61 (16–92)	53 (16–88)
Age at disease onset, years, median (range)	57 (0.2–84)	55 (0.2–72)	58.5 (0.2–84)	57 (0.2–80)	55 (0.2–84)
Disease duration, years, median (range)	8 (0.25–51)	8 (0.58–51)	8.5 (0.25–40)	8 (0.58–51)	8 (0.25–32)
Total number of flares, median (range)	3 (1–25)	3 (1–24)	3.5 (1–25)	3 (1–24)	3 (1–25)
Annual flare frequency, mean (SD)	0.98 (0.93)	1.02 (0.92)	0.91 (0.97)	0.85 (0.70)	1.17 (1.19)
Total number of flares requiring hospitalisation, median (range)	2 (0–24)	2 (0–24)	2 (0–13)	2 (0–24)	2 (0–12)
GPPGA total score for most severe flare, median (range)	3 (1–4)	3 (2–4)	3 (1–4)	3 (2–4)	3 (1–4)
Presence/history of plaque psoriasis, *n* (%)	34 (58.6)	19 (54.3)	15 (65.2)	34 (100)	0
Presence/history of psoriatic arthritis, *n* (%)	16 (27.6)	12 (34.3)	4 (17.4)	10 (29.4)	6 (25.0)
Presence of scalp psoriasis, *n* (%)	13 (22.4)	9 (25.7)	4 (17.4)	12 (35.3)	1 (4.2)
Presence of intertriginous psoriasis, *n* (%)	12 (20.7)	7 (20.0)	5 (21.7)	9 (26.5)	3 (12.5)
Presence of chronic nail psoriasis, *n* (%)	10 (17.2)	5 (14.3)	6 (26.1)	10 (29.4)	1 (4.2)
Presence of Hallopeau-type psoriasis, *n* (%)	8 (13.8)	4 (11.4)	4 (17.4)	4 (11.8)	4 (16.7)
Presence of palmoplantar pustulosis, *n* (%)	7 (12.1)	5 (14.3)	2 (8.7)	5 (14.7)	2 (8.3)
Comorbidities, *n* (%)					
Hypertension	25 (43.1)	15 (42.9)	10 (43.5)	12 (35.3)	13 (54.2)
Hyperlipidaemia	19 (32.8)	9 (25.7)	10 (43.5)	10 (29.4)	9 (37.5)
Cardiovascular disease	15 (25.9)	6 (17.1)	9 (39.1)	7 (20.6)	8 (33.3)
Obesity	10 (17.2)	6 (17.1)	4 (17.4)	5 (14.7)	5 (20.8)
Diabetes	9 (15.5)	7 (20.0)	2 (8.7)	6 (17.6)	3 (12.5)
Depression	8 (13.8)	4 (11.4)	4 (17.4)	5 (14.7)	3 (12.5)
Hypothyroidism	7 (12.1)	7 (20.0)	0	3 (8.8)	4 (16.7)
Hyperuricaemia	7 (12.1)	3 (8.6)	4 (17.4)	3 (8.8)	4 (16.7)
Chronic kidney disease	5 (8.6)	3 (8.6)	2 (8.7)	2 (5.9)	3 (12.5)
History of hepatitis B	5 (8.6)	4 (11.4)	1 (4.3)	5 (14.7)	0
Other	30 (51.7)	19 (54.3)	11 (47.8)	16 (47.1)	14 (58.3)
Trigger factors, *n* (%)[a]					
Infection[b]	20 (34.5)	13 (37.1)	7 (30.4)	9 (26.5)	11 (45.8)
Drug initiation or withdrawal[c]	13 (22.4)	7 (20.0)	6 (26.1)	6 (17.6)	7 (29.2)
Stress	3 (5.2)	2 (5.7)	1 (4.3)	2 (5.9)	1 (4.2)
Other[d]	7 (12.1)	2 (5.7)	5 (21.7)	2 (5.9)	5 (20.8)
Unknown	27 (46.6)	15 (42.9)	12 (52.2)	19 (55.9)	8 (33.3)

Abbreviations: COVID-19, coronavirus disease 2019; GPP, generalized pustular psoriasis; GPPGA, Generalized Pustular Psoriasis Physician Global Assessment; NSAID, non-steroidal anti-inflammatory drug; SD, standard deviation.

[a]Some patients experienced more than one trigger factor for a GPP flare.

[b]Infections were COVID-19, pneumonia, pyoderma, *Staphylococcus aureus* infection, streptococcal tonsillitis, upper respiratory tract infection (*n* = 2), urinary tract infection (*n* = 2), not specified (*n* = 11).

[c]Drug triggers were amoxicillin, amoxicillin/clavulanic acid, beta-blockers, betamethasone, bortezomib + bendamustine + lenalidomide, cefuroxime, chloroquine + sulfasalazine; NSAIDs (Gripex: dextromethorphan, paracetamol, and pseudoephedrine), stopping treatment with systemic steroids (*n* = 2; both patients were female and had concomitant plaque psoriasis), systemic antibiotics, topical imiquimod, not specified.

[d]Other triggers were alcohol, paraneoplastic syndrome, pregnancy (*n* = 3), reappearance of menstruation after a long break, vaccination.

[2 out of 24], $p = 0.463$), respectively (Table 1). The overlap in observed psoriasis subtypes of patients, including patients with (*n* = 34) and without plaque psoriasis (*n* = 24) is shown in Figure 2. A high percentage of palmoplantar pustulosis episodes (85.7% [6 out of 7]) and Hallopeau-type psoriasis (75.0% [6 out of 8]) occurred in individuals who presented with other psoriasis subgroups; however, these conditions did not necessarily occur contemporaneously. Heterogeneity in flare presentation was observed across two separate GPP flare episodes in a male, 69-year-old patient (Figure 3).

Clinical characteristics of 34 patients with GPP who presented with plaque psoriasis at any time during the disease course are shown in Table 2. The presentation of the two

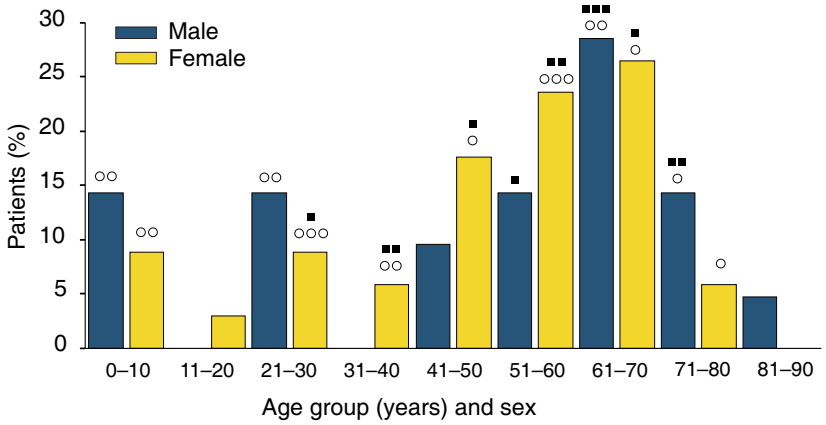

FIGURE 1 Distribution of GPP episodes according to sex and age at GPP diagnosis, indicating any cases with drug or infection triggers*. *Some patients were reported as having both drug and infection triggers. ■ Case of drug trigger (initiation/withdrawal of medication); ○ Case of infection trigger. F, female; GPP, generalized pustular psoriasis; M, male.

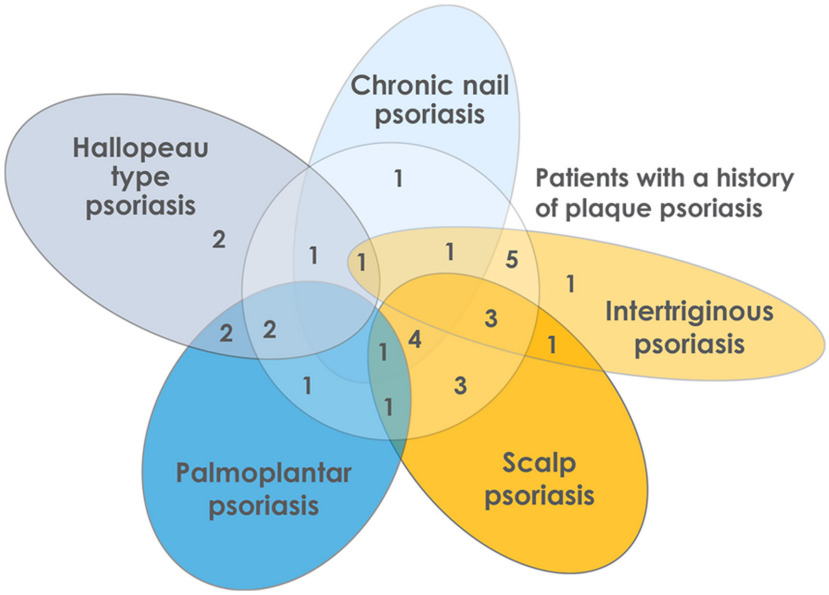

FIGURE 2 Presentation of observed psoriasis subtypes in patients with GPP ($n = 58$), including overlap in patients with a history of plaque psoriasis ($n = 34$; 24 instances) and patients with GPP only ($n = 24$, 6 instances)*. *Instances ($n = 30$) of psoriasis subtypes may not have occurred concurrently. GPP, generalized pustular psoriasis.

diseases varied considerably; a high proportion of patients presented with GPP pustular lesions simultaneously at distant sites from plaques (55.9% [19 out of 34]). Fewer patients presented with plaque-type psoriasis before (47.1% [16 out of 34]) or after (41.2% [14 out of 34]) the first occurrence of pustular lesions. The percentage of BSA affected by plaques in these patients was >10% in 47.1% of individuals (16 out of 34), with a median (range) Psoriasis Area and Severity Index score of 11 (1.6–31; $n = 22$) (Table 2).

Last and most severe flare

Data collected for a patient's last (most recent) flare ($N = 58$) and most severe flare ($N = 58$), which was designated at clinician's discretion from all documented episodes, resulted in an overlap between these categories (Figure S3A). Data are presented throughout for the three subgroups that arose from this overlap: 'historical most severe flare' ($n = 26$), 'last flare: other' ($n = 26$) and 'last flare = most severe flare' ($n = 32$). The supplementary material provides a breakdown of flare details to reflect how CRF data were collected (Figure S3B).

Systemic symptoms and skin symptoms in all flares

A heatmap showing systemic symptoms and GPPGA scores for all 84 individual flare episodes is shown in Figure 4. Systemic symptoms were even present in patients with a GPPGA total score or GPPGA pustulation subscore of 1

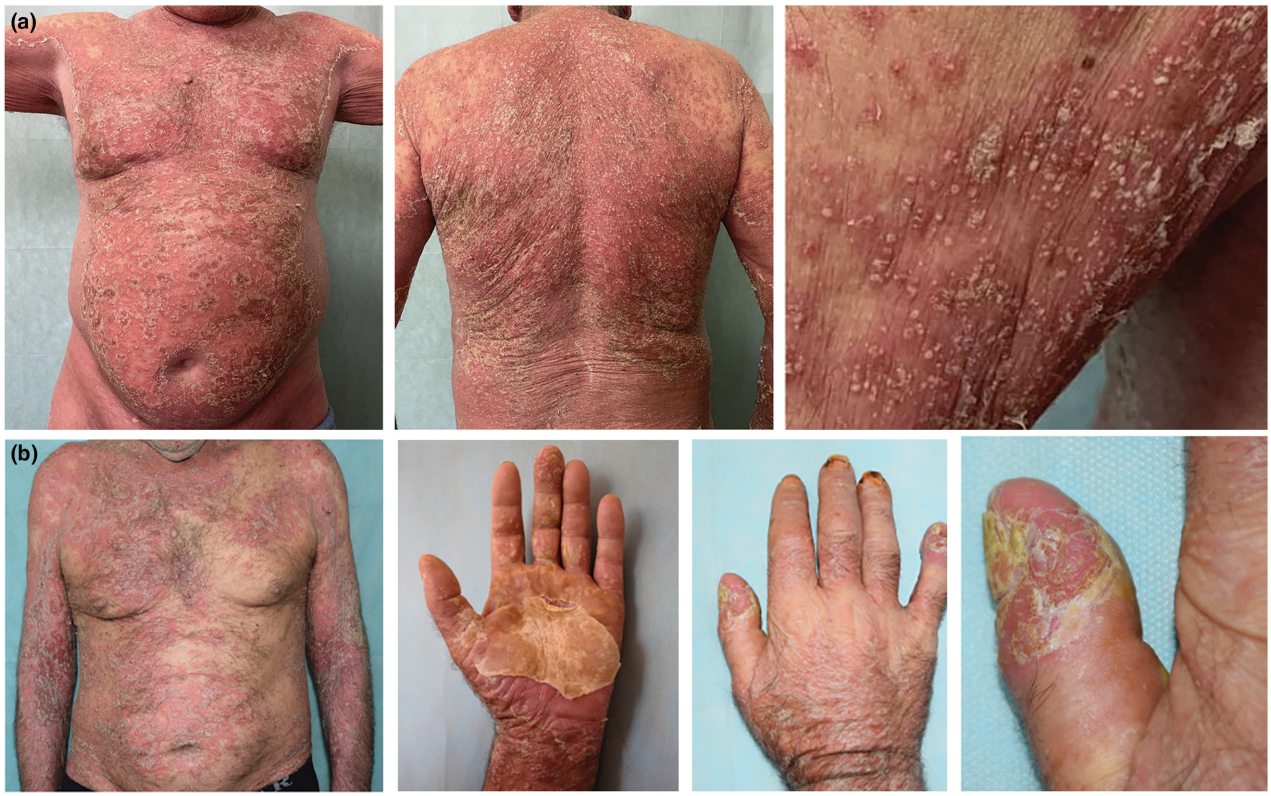

FIGURE 3 Clinical photographs of two separate GPP flare episodes in a male, 69-year-old patient from the study cohort; (a) Generalized erythroderma with multiple pustules observed during the Last = most severe flare*, (b) A less severe flare associated with acrodermatitis continua Hallopeau on the fingertips. *Maximum GPPGA scores observed during the flare: GPPGA total score: 4; GPPGA pustulation subscore: 4; GPPGA erythema scaling subscore: 3; GPPGA scaling subscore: 3. GPP, generalized pustular psoriasis; GPPGA, Generalized Pustular Psoriasis Physician Global Assessment.

TABLE 2 Clinical characteristics of patients with GPP who presented with plaque psoriasis at any time during the disease course ($n = 34$).

Characteristic, *n* (%)	Patients
Plaque-type lesions present at the same time as pustular lesions	16 (47.1)
Patients also suffered from concomitant plaque-type *psoriasis cum pustulatione*	11 (32.4)
Pustular lesions present simultaneously at distant sites from plaques	19 (55.9)
Plaque-type lesions present before the first occurrence of pustular lesions	16 (47.1)
Plaque-type lesions present at any time after the first occurrence of pustular lesions	14 (41.2)
Only plaque-type lesions present in the follow-up at last observation	13 (38.2)
BSA affected by plaques ($n = 32$)	
<3%	3 (8.8)
3%–10%	13 (38.2)
>10%	16 (47.1)
Unknown	2 (5.9)
PASI score, median (range) ($n = 22$)	11 (1.6–31)
Predominant skin type during flare, *n* (%)	($n = 32$)
Plaque type lesions without pustular lesions inside plaques	0
Plaque-type *psoriasis cum pustulatione*	2 (6.3)
Pustular lesions distant from plaques or without plaques	30 (93.8)
Only a few [<3% BSA] chronic plaque type lesions present	16 (50.0)

Abbreviations: BSA, body surface area; GPP, generalized pustular psoriasis; PASI, Psoriasis Area and Severity Index.

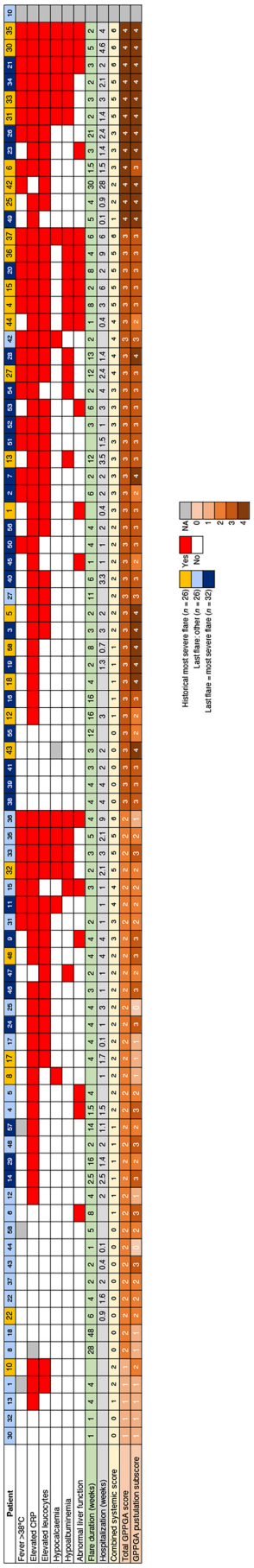

FIGURE 4 Heatmap of patient data for systemic symptoms and GPPGA scores for all individual flares*. *Significant correlations were observed with GPPGA total score ($r = 0.385$, $p < 0.001$), GPPGA pustulation subscore ($r = 0.305$, $p < 0.05$) and duration of hospitalisation ($r = 0.349$, $p < 0.05$). From left to right, data are presented by increasing GPPGA total score (0–4), increasing GPPGA pustulation subscore (0–4), increasing combined systemic disease score (0–7) and patient number (1–58). CRP, C-reactive protein; GPPGA, Generalized Pustular Psoriasis Physician Global Assessment; NA, not available.

or 2 (Figure 4). A significant correlation was observed between combined systemic disease score and both GPPGA total score ($r = 0.385$, $p < 0.001$) and GPPGA pustulation subscore ($r = 0.305$, $p < 0.05$), as well as the duration of hospitalization ($r = 0.349$, $p < 0.05$). GPPGA total score also significantly correlated with levels of CRP ($r = 0.360$, $p < 0.05$) and neutrophils ($r = 0.331$, $p < 0.05$), as did GPPGA pustulation subscore (CRP: $r = 0.332$; neutrophils: $r = 0.320$, $p < 0.05$ for both). Leucocyte levels were not significantly correlated with GPPGA total score ($r = 0.253$) or GPPGA pustulation subscore ($r = 0.259$).

Clinical characteristics of flare subgroups

Patients were more likely to require hospitalization for their historical most severe flare (92.3% [24 out of 26]) and last flare = most severe flare (93.8% [30 out of 32]) compared with last flare: other (57.7% [15 out of 26]; Figure 5). Three patients required ICU care (11.5%) for their historical most severe flare. Median (range) duration of hospitalization was 2.3 (0.4–28.0) weeks in the historical most severe flare subgroup and 1.6 (0.1–9.0) weeks in the last flare: other subgroup. Median (range) percentage of BSA involved was 70% (10%–90%) and 43% (1%–90%), respectively, in these subgroups (Table 3). Median (range) GPPGA pustulation subscores were 3.0 (1–4), 3.0 (2–4) and 2.0 (0–3) for the historical most severe flare, last flare = most severe flare and last flare: other subgroups, respectively. Median (range) GPPGA total score was 3.0 (1–4), 3.0 (2–4) and 2.0 (1–3) for these subgroups (Table 3).

More increases in systemic symptoms, including fever (>38°C), elevated CRP and leucocyte levels (Figure 5) and higher GPPGA scores (Figure 6), were observed in the historical most severe flare ($n = 26$) and last flare = most severe flare ($n = 32$) subgroups compared with the last flare: other subgroup ($n = 26$). The severity of flare symptoms was similar in the historical most severe flare and last flare = most severe flare subgroups. A higher proportion of patients had GPPGA scores of 3 or 4 in the historical most severe flare and last flare = most severe flare subgroups than the last flare: other subgroup (Figure 6). Clinical characteristics of the most severe flare ($N = 58$) and last flare ($N = 58$), as captured by the CRF, are shown in Table S1. A greater proportion of patients presented with systemic symptoms and elevated markers of systemic inflammation during their most severe flare episode compared with their last flare (Figure S4). Distribution of GPPGA total scores and subscores in these groups are presented in Figure S5.

Treatment approach for most severe and last flares

Retinoids were the most frequently used treatment in all subgroups (Table 4), with a higher percentage of biologics used in the last flare = most severe flare subgroup (25.0% [8 out of 32]), compared with the historical most severe

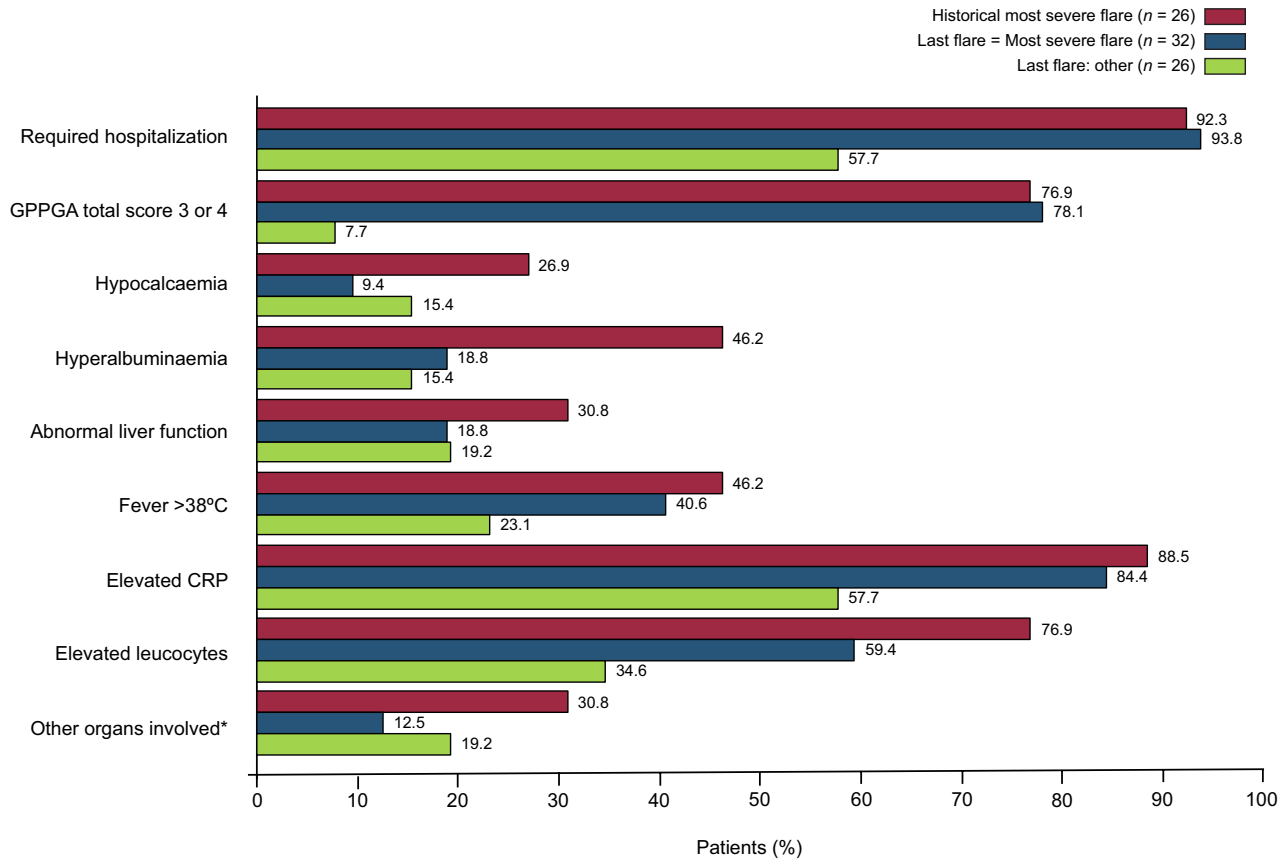

FIGURE 5 Clinical characteristics of flare subgroups. *Other organs involved included acute respiratory distress syndrome, kidney failure, metabolic disorders, osteoarthritis and sepsis. CRP, C-reactive protein; GPPGA, Generalized Pustular Psoriasis Physician Global Assessment.

TABLE 3 Clinical characteristics of 84 individual flares from 58 patients[a].

Clinical characteristic	Historical most severe flare (*n* = 26)	Last flare: other (*n* = 26)	Last flare = most severe (*n* = 32)
Flare duration, weeks, median (range)	4.0 (1.0–30.0)	4.0 (1.0–48.0)	4.0 (1.0–21.0)
Duration of hospitalisation, weeks, median (range)	2.3 (0.4–28.0)	1.6 (0.1–9.0)	2.0 (0.1–4.0)
Percentage of BSA involved, median (range)	70 (10–90)	43 (1–90)	68 (9–90)
GPPGA total score, median (range)	3 (1–4)	2 (1–3)	3 (2–4)
GPPGA pustulation subscore, median (range)	3 (1–4)	2 (0–3)	3 (2–4)
GPPGA erythema subscore, median (range)	3 (1–4)	2 (1–4)	3 (2–4)
GPPGA scaling subscore, median (range)	3 (0–4)	1 (0–3)	2.5 (2–4)
Predominant skin type during flare, *n* (%)	**(*n* = 14)**	**(*n* = 14)**	**(*n* = 18)**
Plaque-type lesions without pustular lesions inside plaques	0	0	0
Plaque-type *psoriasis* cum *pustulatione*	1 (7.1)	1 (7.1)	1 (5.6)
Pustular lesions distant from plaques or without plaques	13 (92.9)	13 (92.9)	16 (94.4)
Only a few [<3% BSA] chronic plaque type lesions present	5 (35.7)	5 (35.7)	11 (61.1)

Abbreviations: BSA, body surface area; GPPGA, Generalized Pustular Psoriasis Physician Global Assessment.

[a]Historical most severe flare and last flare: other represent two different flares recorded in the same patient.

flare subgroup (15.4% [4 out of 26]). Psoralen and ultraviolet light A (PUVA)/ultraviolet B (UVB) phototherapy or systemic steroid use was higher for the historical most severe flare compared with last flare = most severe flare and last flare: other subgroups. Use of cyclosporine treatment was low for both the historical most severe flare (0%) and last flare = most severe flare (9.4% [3 out of 32]) subgroups (Table 4).

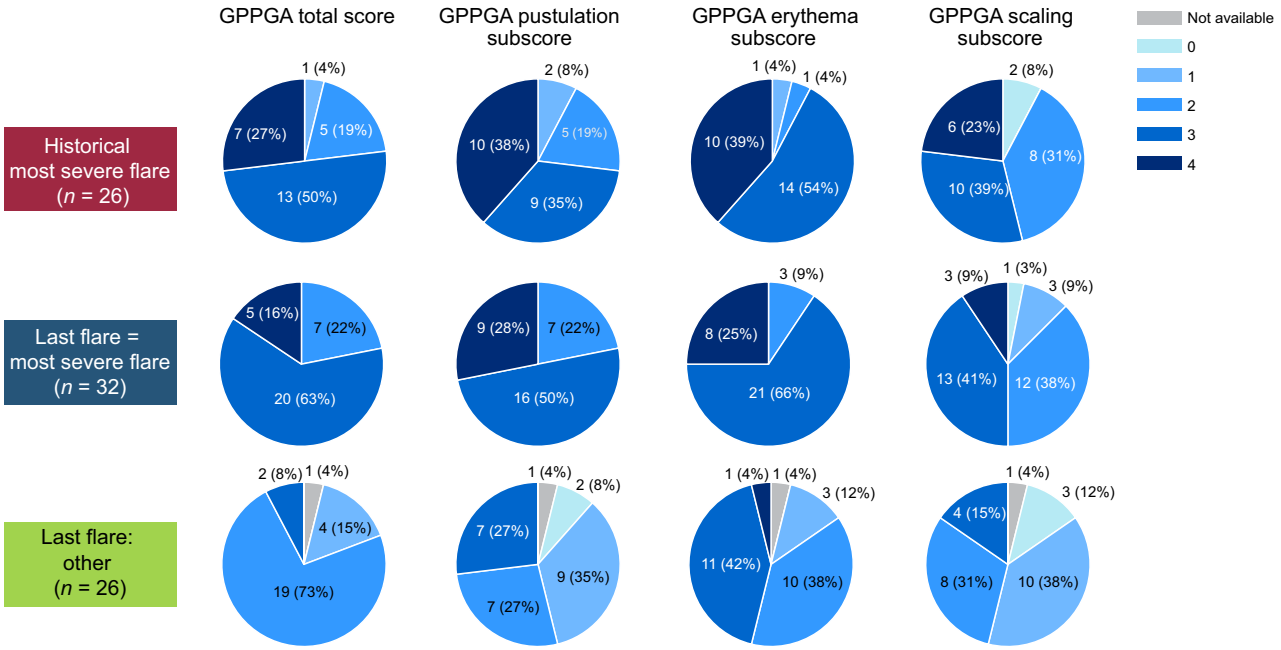

FIGURE 6 Distribution of GPPGA total score and subscores for flare subgroups. GPPGA, Generalized Pustular Psoriasis Physician Global Assessment.

TABLE 4 Summary of treatment types used for the flare subgroups.

Treatment[a], number of patients treated (%)	Historical most severe flare (*n* = 26)	Last flare: other (*n* = 26)	Last flare = most severe (*n* = 32)
Retinoids	14 (53.8)	14 (53.8)	13 (40.6)
Methotrexate	6 (23.1)	5 (19.2)	5 (15.6)
Systemic steroids	6 (23.1)	2 (7.7)	6 (18.8)
PUVA	5 (19.2)	2 (7.7)	4 (12.5)
Biologics	4 (15.4)	9 (34.6)	8 (25.0)
Anti-TNF-α	2 (7.7)	3 (11.5)	4 (12.5)
Anti-IL-12/-23	1 (3.8)	3 (11.5)	0
Anti-IL-17A	0	1 (3.8)	3 (9.4)
Anti-IL-36R	2 (7.7)	1 (3.8)	2 (6.3)
Anti-IL-23A	0	1 (3.8)	2 (6.3)
UVB	4 (15.4)	0	4 (12.5)
Cyclosporine	0	3 (11.5)	3 (9.4)

Note: Retinoids: acitretin or isotretinoin; anti-TNF-α: adalimumab, etanercept or infliximab; steroids: corticosteroids, hydrocortisone, methylprednisolone or prednisone; anti-IL-12/-23, ustekinumab; anti-IL-36R: spesolimab or imsidolimab; anti-IL-17A, ixekizumab or secukinumab; anti-IL-23A, guselkumab, risankizumab or tildrakizumab.

Abbreviations: IL, interleukin; PUVA, psoralen and ultraviolet A phototherapy; TNF-α, tumour necrosis factor alpha; UVB, ultraviolet B phototherapy.

[a]Treatments may have been given as single agents, sequentially and/or as combination therapy; patients may have received multiple treatments.

Individual patient data on treatments received and flare characteristics are shown in Figure S6. Flares were resolved in the majority of episodes (77.4%, [65 out of 84]). Median (range) time from treatment initiation to flare resolution was comparable across all subgroups: historical most severe flare, 4 (1–16) weeks; last flare = most severe flare, 4 (0.1–52) weeks; and last flare: other, 4 (1–54) weeks. Treatment types for last flare ($N = 58$) and most severe flare ($N = 58$), as collected by the CRF, are summarized in Table S2.

DISCUSSION

We present data from a large cohort of patients with GPP from the CEE region, providing much-needed information on the clinical presentation and treatment landscape of GPP and contributing to current knowledge of this complex, unpredictable and potentially life-threatening disease. During GPP flares, patients experienced cutaneous symptoms affecting at least 40% of the BSA, often accompanied by fever and other systemic symptoms. GPP is phenotypically,

genetically and histopathologically distinct from plaque psoriasis and may or may not be preceded by a history of plaque psoriasis.[4,12] In line with previous data,[7] over half of patients (58.6%) had a history/comorbidity of plaque psoriasis, highlighting the importance of distinguishing between the two conditions to ensure appropriate patient care. Patient demographics were generally similar between sexes and between those with and without a history of plaque psoriasis. Comorbidities, including hypertension and hyperlipidaemia, were reported at higher percentages than in previous GPP populations,[7] which is likely due to the increased age of this cohort (most patients aged >60 years) compared with other studies.[7,10,35,36] High hospitalization rates (>90%) were observed in flares classified as severe by clinicians. Duration of GPP flares and hospitalization, and annual frequency of flares, were comparable to published reports.[6,35–38]

Here, GPP diagnosis was validated according to ERASPEN criteria[2]; 80.4% of patients had GPP confirmed by skin biopsy (45 out of 56) to corroborate physician diagnoses. Current ERASPEN guidelines define GPP as primary, sterile, macroscopically visible pustules on non-acral skin.[2] We observed an overlap in the presentation of psoriasis subtypes with GPP. Although not necessarily concurrent with GPP, the presentation of conditions such as palmoplantar pustulosis and Hallopeau-type psoriasis, which can manifest on the acral skin, suggests that the ERASPEN guidelines for GPP, which exclude non-acral skin, could be revised and expanded based on our findings.

A number of tools to measure disease activity in patients with GPP have recently been developed and implemented in clinical trials, including the GPPGA and the Generalized Pustular Psoriasis Area and Severity Index.[25,33,39] Considerable variation in GPPGA scores was observed in all patient subgroups, highlighting the unpredictable nature of GPP flares. Variation was also observed in the severity of systemic inflammatory symptoms, and the disparity between the clinical features of two different GPP flares in the same patient further emphasizes the heterogeneous nature of the disease. Correlation analysis revealed a significant association between a patient's combined systemic disease score and both GPPGA total score and GPPGA pustulation subscore. These data suggest that a high GPPGA score is associated with an increased likelihood of systemic symptoms.

Considerable variation was observed in the type of treatment received by patients with GPP. Many patients were treated with retinoids and PUVA/UVB, and the use of cyclosporine was low compared with other studies.[40] Tumour necrosis factor (TNF)-inhibitors have been shown to trigger GPP in rare cases the disease,[36] however we made no such observations in our cohort. Assuming the medications used in the last flare = most severe flare subgroup represent the current treatment landscape for GPP, the increased use of biologics in this subgroup compared with the historical most severe flare subgroup would indicate that the use of biologics is increasing and may reflect a shift in clinical approach. The time to resolution of flares after treatment initiation was slow in all patient subgroups (median 4 weeks), highlighting an unmet need for treatments that provide rapid and sustained pustular and skin clearance.

The results presented are limited to the information provided by the medical records and extracted into the CRF. In addition, data on a patient's most severe flare were recorded at clinician's discretion, and the lack of predefined criteria to classify the severity of these episodes or measures of response is a further limitation of the study. Indeed, the overlap between last and most severe flares resulted in a variable dataset, with information for two separate episodes in the same patient provided by less than half (26 out of 58) of the study cohort.

Even acknowledging these limitations, the results highlight the considerable heterogeneity in the presentation of GPP flares, both between patients and within a patient. Even GPP flares with low GPPGA scores manifest a significant clinical burden, highlighting the unmet need for accurate and early diagnosis to allow prompt treatment and avoid prolonged hospitalization. While mortality rates of 2%–16% have been reported for GPP,[41] we observed no deaths in our study cohort. Further investigation is required to determine if this is due to improved early diagnosis of the disease, better treatment strategies and/or the increased use of biologics in recent years. The recent approval of spesolimab, an IL-36-targeted therapy, provides the strongest evidence to date of efficacy for the treatment of GPP flares and opens the possibility of further exploring such therapies as a means of preventing flares.

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CONFLICT OF INTEREST STATEMENT

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DATA AVAILABILITY STATEMENT

Scientific and medical researchers can request access to the anonymized study data by contacting Professor P. Wolf, peter.wolf@medunigraz.at.

ETHICS STATEMENT

The study was conducted in accordance with the ethics and institutional regulations of each participating centre. The study protocol (approval no. 21-094 ex 09/10) and CRF (approval no. 34-290 ex 21/22) used in the study were approved by the ethics review committee of Medical University of Graz. The patients in this manuscript have given written informed consent to publication of their case details.

ORCID

P. Wolf https://orcid.org/0000-0001-7777-9444
R. Ceovic https://orcid.org/0000-0002-1296-6174
C. Conrad https://orcid.org/0000-0002-2547-3440
K. Falkensteiner https://orcid.org/0000-0002-8044-2727
T. Graier https://orcid.org/0000-0002-3007-7776
M. Marovt https://orcid.org/0000-0003-1954-1416
V. Mateeva https://orcid.org/0000-0002-4694-4977
J.-T. Maul https://orcid.org/0000-0002-9914-1545
A. A. Navarini https://orcid.org/0000-0001-7059-632X
A. C. Nicolescu https://orcid.org/0000-0003-4828-464X
G. Ratzinger https://orcid.org/0000-0002-9860-6697
L. Pavlovsky https://orcid.org/0000-0001-8400-9587
A. Szegedi https://orcid.org/0000-0003-2109-9014
A. Reich https://orcid.org/0000-0002-5573-1754

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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