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REVIEW ARTICLE

# Clinical Course and Characteristics of Generalized Pustular Psoriasis

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## Abstract

Generalized pustular psoriasis (GPP) is a rare, potentially life-threatening disease characterized by episodes of widespread sterile macroscopic pustules, with or without systemic inflammation and/or plaque psoriasis. Multiple GPP subtypes have been described, from acute GPP of von Zumbusch to milder, annular pustular psoriasis. Generalized pustular psoriasis mainly affects adults, with a female preponderance, but juvenile GPP also occurs. Flares are a hallmark of GPP and may occur de novo or be provoked by triggers, including withdrawal of systemic corticosteroids, infections, stress, pregnancy, and menstruation. Severity of flares varies widely between patients, and between flares in an individual patient. Significant flares are often accompanied by systemic symptoms, notably fever, general malaise, and extracutaneous manifestations such as arthritis, uveitis, and neutrophilic cholangitis. Common laboratory abnormalities include neutrophilia, elevated C-reactive protein levels, hypocalcemia, and abnormal liver function tests. The clinical course of GPP is highly variable; it can be a relapsing disease with recurrent flares and no pustulation between flares or a persistent disease with perpetual mild pustulation punctuated with flares of greater severity. Patients may have multiple flares per year or a flare every few years. Most flares last 2–5 weeks and approximately 50% require hospitalization. Life-threatening complications include sepsis and renal, hepatic, respiratory, and heart failure. Reported mortality rates are 2–16%.

**Key Points**

Flares of generalized pustular psoriasis vary in frequency, severity, and length between patients and between flares in the same patient.

Generalized pustular psoriasis flares may occur de novo or be triggered by external factors, including stress, infections, and withdrawal of medication.

## 1 Introduction

Generalized pustular psoriasis (GPP) is a rare and potentially life-threatening auto-inflammatory disease characterized by recurrent episodes of widespread painful erythema with sterile pustules and "lakes of pus" on non-acral skin [1, 2]. Generalized pustular psoriasis flares are usually accompanied by systemic symptoms, specifically high fever, general malaise, fatigue, and disabling edema [3]. Common extracutaneous manifestations include arthritis, uveitis, and neutrophilic cholangitis [3]. Generalized pustular psoriasis flares are often provoked, and common precipitating factors include withdrawal of systemic corticosteroid therapy, infections, pregnancy, menstruation, and stress [2–5]. Laboratory abnormalities associated with GPP flares comprise neutrophilia, elevated C-reactive protein (CRP) levels, hypocalcemia, hypoalbuminemia, and abnormal liver function tests [3, 6–8]. Potentially life-threatening complications include sepsis and renal, hepatic, respiratory, and heart failure [6, 7, 9]. Reported mortality rates are between 2 and 16% [3, 4, 10].

Generalized pustular psoriasis is a heterogeneous disease with a highly variable clinical course. The extent and severity of symptoms vary between patients, as well as between each flare experienced by an individual patient. A flare may

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affect minimal or extensive areas of the skin. While some patients have multiple severe flares per year, others may only experience a flare every few years. Few studies have explored the clinical course of GPP owing to its rarity, its heterogeneous nature, and the lack of a universally accepted definition of a flare. Distinct phenotypes of GPP are well documented, but there is little agreement on the classification of these clinical variants [1, 3–5, 11]. The clinical course of these variants is largely unknown, although the clinical manifestations of GPP may change from one phenotype to another over time in the same patient.

This article provides an overview of the clinical characteristics and course of GPP, based on the available published data, supplemented by representative patient case reports to illustrate the heterogeneity of this rare disease. The diagnosis [12] and treatment [13] of GPP are discussed in accompanying reviews within this supplement.

## 2 Clinical Characteristics and Course of GPP

### 2.1 Clinical Variants of GPP

Generalized pustular psoriasis was first reported in 1910 by Leopold von Zumbusch, who described a patient with plaque psoriasis who experienced nine episodes of widespread pustular eruption over a period of 20 years [14]. Although there have been multiple subsequent case reports and series of GPP, few have included more than 100 patients. The earliest and largest case series with a detailed clinical review included 104 patients and was published in 1968 [4]. The authors classified GPP into four clinical variants: acute GPP of von Zumbusch, annular pustular psoriasis (APP), localized GPP, and exanthematic GPP.

Annular pustular psoriasis is a less acute variant of GPP and is characterized by a subacute or chronic eruption of annular or serpiginous plaques with erythematous scaly or pustular margins [15]. Patients are usually constitutionally well, without fever, leukocytosis, arthritis, or other organ involvement. Common aggravating factors are stress, upper respiratory tract infections (URTIs), and menstruation [15–17]. Annular pustular psoriasis is a more benign variant of GPP that responds to topical agents; however, severe juvenile APP that does not respond to conventional systemic therapy and develops into acute GPP has been documented [15].

Baker and Ryan described localized GPP as pustulosis that occurs in and around discoid psoriatic plaques [4]. The most common trigger is superimposed bacterial infection and pustules usually resolve promptly with systemic antibiotics. Localized GPP is widely recognized as a variant of plaque psoriasis called psoriasis with pustulosis or "psoriasis cum pustulatione" as it is not uncommon for patients with psoriasis vulgaris to have pustular lesions during periods of heightened disease activity, particularly following a URTI [18] or the use of irritant topical agents [19].

Exanthematic GPP was described as a sudden onset of sterile pustules in patients with no previous history of psoriasis [4]. It usually follows a URTI or use of systemic medications for treating a URTI. Exanthematic GPP is self-limiting and resolves completely within a few weeks. This description is reminiscent of acute generalized exanthematous pustulosis (AGEP); therefore, most dermatologists accept exanthematous GPP as AGEP. The prevalence of psoriasis is higher in patients with AGEP than in the general population [20]. Both AGEP and GPP are associated with *IL36RN* mutations and patients with interleukin-36 receptor antagonist insufficiency have a severe form of AGEP [21].

Despite being first described 110 years ago, there is still no international consensus on the definition of a GPP flare or the different phenotypes. In 2017, the European Rare And Severe Psoriasis Expert Network (ERASPEN) published their consensus definition of pustular psoriasis, which defined GPP as macroscopic primary sterile pustules occurring on non-acral skin. It excludes cases in which pustules are restricted to within psoriatic plaques [1]. Generalized pustular psoriasis should only be diagnosed when the condition has relapsed at least once or when it persists for more than 3 months [1], and AGEP should be actively ruled out. Generalized pustular psoriasis can occur with or without plaque psoriasis, and with or without systemic inflammation. Under ERASPEN criteria, APP is classified as the chronic variant, with pustulation persisting for more than 3 months, and usually occurs without systemic symptoms or associated psoriasis vulgaris. Impetigo herpetiformis, or pregnancy-induced GPP, is now believed to be the same disease as acute GPP because the majority of patients have other triggers in addition to pregnancy [3, 22, 23].

### 2.2 Clinical Characteristics of GPP

Generalized pustular psoriasis is a severe disease that affects both children and adults. Table 1 shows clinical characteristics of patients with GPP from notable case series and analyses of healthcare systems and records. Approximately 31–78% of patients with GPP have preceding psoriasis [17, 24], with a pre-pustular duration in some patients of ≥ 20 years [4]. Onset of GPP occurs earlier in patients without preceding psoriasis [4, 17, 25]. Generalized pustular psoriasis flares are often provoked. Common precipitating factors include infections (particularly URTIs), sunlight, pregnancy, menstruation, hypocalcemia, and a long list of systemic drugs [26]. Excessive use of irritant topical preparations, such as coal tar, may induce GPP and the use of potent topical corticosteroids has also been implicated [26]. However, the most common precipitating factor is

**Table 1** Comparison of patient demographics and GPP clinical characteristics and outcomes in studies reporting > 25 patients with adult-onset GPP and > 15 patients with juvenile GPP, and with sufficient and/or relevant data to tabulate results

| Characteristic | Choon [3] (Malaysia) $N = 102$ | Baker [4] (UK) $N = 104$ | Ohkawara [25] (Japan) $N = 208$ | Zelickson [5] (USA) $N = 63$ | Tay [33] (Singapore) $N = 28$[a] | Borges-Costa [46] (Portugal) $N = 34$ | Jin [11] (Korea) $N = 33$ | Hela [47] (Tunisia) $N = 44$ | Huang [48] (Taiwan) $N = 39$[b] | Popadic [49] (Serbia) $N = 18$[b] | Lau [17] (Malaysia) $N = 27$[b] |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Male:female | 34:68 | 43:61 | 88:120 | 31:32 | 12:16 | 21:13 | 15:18 | 21:23 | 23:16 | 10:8 | 11:16 |
| Mean age of GPP onset, years | 40.9 | > 40[c] | 33.6 | 43.0 | 37.5 | 58[d] | 40.7 | 20.5 | 6.4[e] | 3.8 | 6.5[d] |
| History of plaque psoriasis, *n* (%) | 79 (77.5) | 62 (59.6) | 65 (31.3) | 32 (50.8) | 3/7[f] (42.9) | 22 (64.7) | 10[f] (40) | 14 (31.8) | 12 (31) | 7 (38.9) | 10 (37.0) |
| Mean pre-pustular duration, years | 11.7 | [g] | 6 | 12[h] | | 11.2 | | | | | |
| Patients with triggers identified, *n* (%) | 87 (85.3) | 54 (51.9) | | 16/35[f] (45.7) | 6/7[f] (85.7) | | 20 (60.6) | | 16 (41) | | 16/21[f] (76.1) |
| Fever, *n* (%) | 94 (92.2) | | | | 7/7[f] (100) | | 8 (24.2) | | [i] | | 17/21 (80.9) |
| Malaise/fatigue, *n* (%) | | | | | 7/7[f] (100) | | | | | | |
| Leukocytosis, *n* (%) | 68 (66.7) | | | | 2/7[f] (28.6) | | 21/29 (72.4) | | [i] | | 13/18[f] (72.2) |
| Arthritis, *n* (%) | 35 (34.3) | 33 (32) | | | | | | 7 (31.8) | | 0 | |
| Mortality, *n* (%) | 7 (7) | 17 (16)[j] | | 2 (3) | 1 (4) | 2 (6) | 1 (4) | 1 (2.3) | | 0 | 0 |

Two additional studies report data for a large number of patients with GPP, but with insufficient information to present in the table. Augey et al. [10] questioned dermatologists and reported on 99 patients with GPP with a male:female ratio was 0.77; the mean age of incident cases was 59.7% and a mortality rate of 2% was indicated. Miyachi et al. [38] reported on 1516 patients with GPP, of whom 853 were male and 663 were female; a mortality rate of 4.2% was indicated)

Blank cells indicate when data are not presented (or not presented in a calculable format) in the cited study. Individual overall study populations may include different forms of GPP, including juvenile GPP or other pustular disease

*GPP* generalized pustular psoriasis

[a]Includes five patients with palmoplantar pustulosis and four patients with acrodermatitis continua of Hallopeau

[b]Study of pediatric patients with GPP/patients with juvenile onset

[c]Three-quarters of patients were aged over 40 years at diagnosis

[d]Mean age at admittance to the hospital ward

[e]Median age of diagnosis

[f]Data for patients with acute GPP only

[g]Baker and Ryan did not provide a mean pre-pustular duration, but for patients with preceding psoriasis "many patients [passed] 10 or 20 or more years before GPP developed" [4]

[h]Among patients with psoriasis preceding acute GPP (24/35 patients)

[i]28/31 patients with GPP presented with systemic inflammation

[j]Mortality data presented by Ryan and Baker, using the same patient cohort [40]

the withdrawal of systemic corticosteroids [27], which is reported in up to 20% of patients with GPP [28]. Other systemic drugs reported to provoke GPP include, but are not limited to, lithium, progesterone, phenylbutazone, antimalarials, fluoxetine, ustekinumab, infliximab, adalimumab, and apremilast [26, 29]

Rebound of psoriasis with novel pustulation is well documented following treatment withdrawal of systemic corticosteroid therapy as well as non-corticosteroid therapy in patients with classic plaque psoriasis [26, 27, 29–31]. For example, Khemis et al. [31] reported that 13.7% of 139 patients taking brodalumab experienced a rebound of psoriasis 12 weeks after stopping brodalumab. All 19 patients had pustular lesions, but only two patients had extensive lesions with associated fever, fatigue, elevated CRP, and leukocytosis. Pustular flares on withdrawal of brodalumab may be attributable to heightened disease activity following rebound of psoriasis on treatment cessation and this may also partly explain the occurrence of GPP following corticosteroid withdrawal.

Generalized pustular psoriasis is characterized by recurrent flares of widespread, painful, fiery erythema studded with sterile pustules that may coalesce to form lakes of pus. Mucosal involvement may also occur, and manifests as cheilitis, geographic tongues or fissured tongues, and genital lesions [32]. Severity can range from mild to severe, and an individual patient can experience different disease extent, severity, and cutaneous and extracutaneous symptoms with each flare. Generalized pustular psoriasis flares may or may not be accompanied by systemic symptoms, including fever, general malaise, fatigue, and disabling edema [26]. Common laboratory abnormalities observed in GPP flares include leukocytosis and neutrophilia, elevated CRP levels, hypocalcemia, hypoalbuminemia, and abnormal liver function tests [3, 6–8].

High fever has been reported in approximately 24–96% of patients during a GPP flare (Table 1) [3, 8, 11] and approximately 30–70% of patients have leukocytosis with neutrophilia recorded [3, 11, 33]. There is no international consensus on the definition of a severe GPP flare. In a single-center study of 95 patients with acute GPP affecting > 30% of the body surface area (BSA), pain, fever, and leukocytosis were prevalent and documented in 96.8%, 95.8%, and 82.1% of patients, respectively [3]. Hence, a GPP flare affecting > 30% BSA may be classified as a severe or significant flare because of its association with systemic inflammation. Systemic inflammation, defined as a fever > 38 °C with leukocytosis > $12 \times 10^9$/L, is more prevalent in patients with *IL36RN* variants [20, 22]. Patients with homozygous *IL36RN* variants have a more severe phenotype that is characterized by early onset, low prevalence of plaque psoriasis, and a high risk of systemic inflammation [34]. Extracutaneous manifestations of a GPP flare include arthritis and arthralgia, uveitis and conjunctivitis, and neutrophilic cholangitis [3, 4, 8, 35]. Generalized pustular psoriasis is also associated with multiple comorbidities, such as hyperlipidemia, hypertension, diabetes mellitus, obesity, anxiety, and depression [3, 32, 36].

### 2.3 Clinical Course of GPP

Generalized pustular psoriasis is an unpredictable disease with a highly variable course. While some patients exhibit multiple flares per year, others may only experience a flare every few years. In the single-center study of 95 patients with a GPP flare affecting > 30% BSA, 56.8% of patients had only one flare, 29.5% had two to five flares, and 13.7% had more than five flares over an average follow-up duration of approximately 5 years [3]. However, 70% of the patients with only one severe flare experienced multiple mild flares on attempts to taper off systemic therapy or when exposed to classic triggers such as URTI, stress, and menstruation, despite receiving systemic therapy [3]. Furthermore, 30% of these patients had persistent pustular lesions and fewer than 5% had clear or almost clear skin between GPP flares. A study using the French National Health Data System (SNDS) database also showed that most patients with GPP had no flare or one flare per year during the study period (between 2010 and 2018) [9]. In this study, most (79.4%) of the 569 patients with incident GPP had only one flare, 17.6% had two to four flares, and 3% had five or more flares. This observation was confirmed by a survey of dermatologists contributing data to the Corrona registry, which showed that most (69%) of the 29 dermatologists surveyed estimated that their patients had an average of no flare or one flare per year and 28% estimated that their patients had an average of two to three flares per year [37].

Generalized pustular psoriasis flares typically last 2–5 weeks but may persist longer than 3 months [3, 11, 37]. Approximately one-third of patients have persistent pustular lesions, even when receiving systemic therapy that resolved the acute symptoms [3]. Persistence of pustular manifestations appears to be greater among patients with APP than those with GPP. In a Korean study, pustular lesions persisted beyond 2 months in 60% of five patients with APP compared with 27% of 15 patients with GPP [11]. It is estimated that up to 10% of patients may not respond to treatment and experience persistent flare [24]. Furthermore, few patients achieve clear skin between flares, despite receiving various treatments [3, 27, 37]. Patients may have psoriasis vulgaris, inverse or erythrodermic psoriasis, APP, and acrodermatitis continua of Hallopeau between GPP flares [3, 11, 25].

Generalized pustular psoriasis flares can be severe and potentially life threatening. An estimated 50% of GPP flares require hospitalization [38] and a patient with GPP will require hospitalization for a flare at least once every

5 years [3]. The duration of inpatient stay for a GPP flare is reported to be 10–14 days [39]. The mortality rate directly attributable to GPP or its associated treatment, specifically with the use of systemic corticosteroids, has been reported to be 2–16% [3, 4, 10, 38]. A recent study from Japan using a national inpatient database showed an overall in-hospital mortality rate of 4.2% among 1513 patients with GPP [38]. The mortality rate was highest in patients receiving systemic corticosteroid monotherapy and lowest in patients receiving biologics, at 9.1% and 1.0%, respectively [38].

## 3 Case Studies

The following case reports illustrate the heterogeneity of GPP, which has a wide spectrum of disease severity and a highly variable clinical course. There is a lack of robust evidence to guide treatment decisions. Treatment instituted for these cases was based on evidence from case series and open-label single-arm studies [40–45]. Treatment options for GPP are discussed in more detail in Chapter 6 of this supplement [13].

### 3.1 Case 1: GPP affecting < 30% BSA

Patient 1 is a 29-year-old Chinese woman whose psoriasis started as scalp lesions that extended beyond her hairline in 2006, when she was 15 years old. Her plaque psoriasis was well controlled with topical corticosteroid therapy, but 1 year later she noticed multiple patches of painful erythema studded with pustules on her trunk (Fig. 1a–c), intergluteal fold, and limbs, at which time she was diagnosed with GPP. She was otherwise well, with no systemic symptoms. The pustular lesions resolved with topical corticosteroid therapy but recurred promptly during menstruation or when she had a URTI. She was distressed by her painful skin lesions and

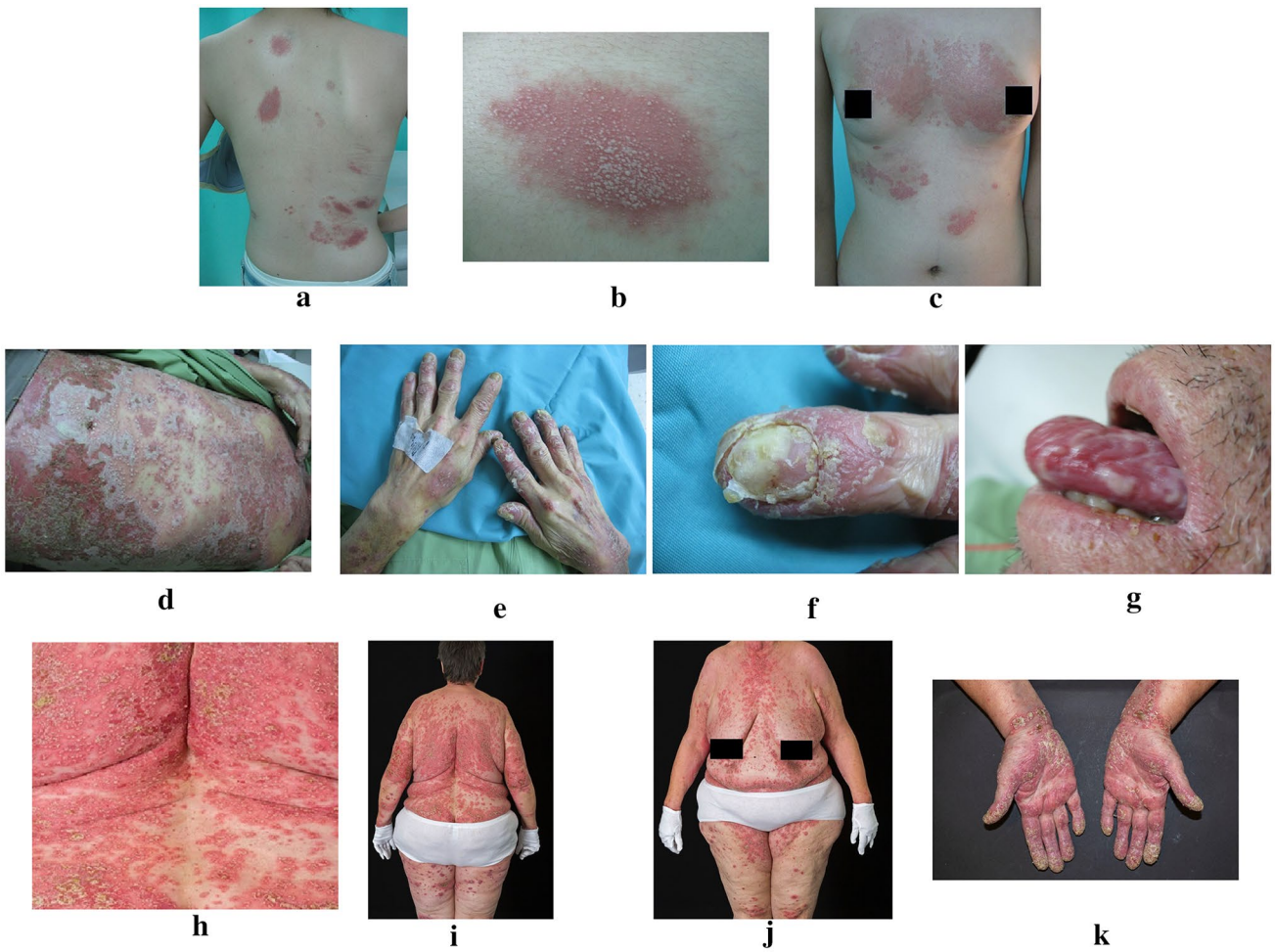


**Fig. 1** Images from the patient cases, showing: scattered erythematous plaques with sterile pustules (**a**) and dense collection of pustules with minimal coalescence (**b**) on the back, and scattered erythematous plaques with pustules on the chest and abdomen (**c**) of patient 1; widespread lesions (**d**) and involvement of the hands (**e**), nails (**f**), and mouth and tongue (**g**) of patient 2; and confluent pustulation (**h–j**) and palmar involvement (**k**) of patient 3

abnormal nails, which displayed pitting, onycholysis, and discoloration. Her quality of life was severely affected, as indicated by her 6-monthly Dermatology Life Quality Index score of between 12 and 20.

She developed arthritis in 2017 when she was 26 years old. Her arthritis and skin lesions improved with oral methotrexate 12.5–15.0 mg weekly, but she was unable to tolerate the associated adverse events, specifically nausea, vomiting, and headache, even when methotrexate was administered subcutaneously. Methotrexate was stopped after 1 year and secukinumab 150 mg every 4 weeks was started in 2018. Her skin lesions, including scalp psoriasis and arthritis, improved but she only achieved sustained clear skin without relapse during menstruation after 2 years of secukinumab therapy.

She currently has clear skin, with only post-inflammatory hyperpigmentation, no scalp lesions, and no arthritis while receiving secukinumab 150 mg every 4 weeks. She does not harbor an *IL36RN* variant but has a *CARD14* variant (p.Asp176His substitution). She has no family history of psoriasis.

### 3.2 Case 2: GPP that Succumbed to Sepsis

Patient 2 was a Chinese man who was first admitted to our hospital in 2013, aged 42 years. Psoriasis started on his scalp in 2007, when he was 36 years old. Subsequently, he developed a few lesions on extensor prominences that were well controlled by topical corticosteroids. With treatment, his lesions were mainly limited to the scalp for about 5 years. He could endure the pruritus and discomfort of his scalp lesions but was embarrassed by the associated abnormal nails.

The patient was lost to follow-up for 1 year. During that year he visited multiple general practitioners and physicians offering traditional Chinese medicines. His scalp psoriasis continued to remit and relapse. He was distraught by the increasing number of abnormal nails despite completing multiple courses of anti-fungal drugs prescribed by his general practitioners. One month before admission to our hospital, he noticed psoriasis on his stomach and thighs. Two weeks prior to admission, he also reported periungual erythema and swelling associated with small pustules under his dystrophic nails and finger pulps. Three days before admission, he had multiple painful pustules on his abdomen and thighs. He was initially admitted to his local hospital where intravenous cloxacillin (500 mg, every 6 h) was promptly started, but his skin lesions worsened rapidly with persistent fever and he was transferred to our hospital for sepsis 2 days later. He did not have cough, chest pain, shortness of breath, nausea, vomiting, or diarrhea, and had no urinary symptoms. He also had no arthritis or comorbidities. He was a chronic smoker but non-drinker. His paternal aunt has plaque psoriasis.

On admission to our hospital, he was alert but in pain with mild bilateral ankle edema, high fever (39.1 °C), and tachycardia (108 beats/min). He had widespread tender erythema with pustules and lakes of pus affecting approximately 50% BSA (Fig. 1d), including lesions on his genitalia, palms, soles, and nails (Fig. 1e, f). He had geographic and fissured tongue and pustules on his upper and lower lips (Fig. 1g). Laboratory abnormalities included leukocytosis ($13.7 \times 10^9$/L; normal range $4.0–11.0 \times 10^9$/L), neutrophilia ($10.4 \times 10^9$/L; normal range $2.0–5.0 \times 10^9$/L), elevated CRP levels (31.21 mg/L; normal range 0–5.0 mg/L), and erythrocyte sedimentation rate (28.0 mm/h; normal range 2.0–7.0 mm/h). Liver function was normal except for a slightly low albumin level and a slightly high alkaline phosphatase level. Renal function and serum calcium were normal. Blood and skin cultures performed on admission were negative. A biopsy taken from a lesion on his back showed typical histologic features of GPP, namely parakeratosis, regular acanthosis, and thinning of the suprapapillary epidermis, with Munro and Kogoj micro-abscesses. Cyclosporin (100 mg twice daily) was initiated in combination with intravenous cefuroxime (1.5 g three times daily).

The patient continued to develop new waves of pustulation until day 4 of admission, increasing the affected area to about 80% BSA. His fever settled on day 5 but recurred on day 7 and his hemoglobin level dropped during admission from 12.3 g/dL (normal range 12.0–17.0 g/dL). Leukocytosis peaked on day 2 ($23.0 \times 10^9$/L), normalized by day 5 ($10.2 \times 10^9$/L), but increased again on day 8 ($15.3 \times 10^9$/L). His liver function became abnormal, with elevated alanine transaminase levels (160 IU/L; normal range 29–33 IU/L) and alkaline phosphatase levels (210 IU/L; normal range 44–147 IU/L), and he developed significant hypoalbuminemia (20 g/L; normal range 35–50 g/L).

On day 7, he was seen by an infectious disease specialist for hospital-acquired infection. Although he did not have cough, crackles on the left lower zone of his lung were detected and intravenous piperacillin/tazobactam (4.5 g four times daily) was started for hospital-acquired infection and cyclosporine was stopped. An abdominal ultrasound was unremarkable, but a chest X-ray showed haziness of right and left lower zones. Within 24 h, his respiratory function deteriorated markedly, with tachypnea and arterial hypoxia, and he was transferred to an intensive care unit and ventilated. The patient continued to have spiking fever and died as a result of sepsis with multiorgan failure after 4 days in the intensive care unit. Multiple blood cultures were negative. A blind bronchoscopic aspirate sample taken on day 7 showed *Corynebacterium* species, coagulase negative *Staphylococcus*, and *Candida* species.

### 3.3 Case 3: Varying Presentation of GPP Flares in an Individual

Patient 3 is a 64-year-old Caucasian woman with a > 10-year history of plaque psoriasis in addition to GPP. Her plaque psoriasis is typically mild to moderate in severity and affects the scalp and flexors of the extremities. She is treated with topical therapies (including betamethasone and calcipotriol) and basic care, which are usually sufficient to provide clear or almost clear skin and cessation of itch. She also has hypertension, which is managed with angiotensin-converting enzyme inhibitors (ramipril, 5 mg once daily) and diuretics (torasemide, 5 mg once daily). She has a family history of plaque psoriasis, but no family member has GPP. Generalized pustular psoriasis flares occur approximately 1–2 times per year and are typically mild (2–3% BSA involvement) to moderate (≤ 10% BSA involvement). The causes of her GPP flares are unknown.

Her mild flares are typically treated with clobetasol cream (0.1%) and moderate flares with retinoids (isotretinoin, up to 30 mg daily) in combination with ultraviolet radiation (narrowband ultraviolet [311 nm], with dosage increased during the first ten treatments to a total of up to 30 treatments within a 2-month period). Some flares, especially those that are more severe, have been associated with a short period (3–5 days) of (sub)erythroderma and multiple pustules formed within 48 h, which subsequently become confluent (Fig. 1h–j). For more severe flares, she is also treated with prednisolone (50 mg once daily, for up to 3–4 weeks, with down tapering) or cyclosporine (up to 5 mg/kg bodyweight for 4–6 weeks).

The patient was hospitalized for at least 14 days for the treatment of her GPP flares. In general, the severe flares were accompanied by a deterioration in her general condition. During her last hospitalization, her flare was accompanied by arthralgia, leukocytosis ($15 \times 10^9$/L), and increases in CRP (18.4 mg/dL) and lactate dehydrogenase levels (286 U/L, from 247 U/L). She was treated with cyclosporine (350 mg daily) in combination with flumethasone (0.2%) plus clioquinol (3%). There were no signs of acute bacterial or viral infection. Furthermore, the palmoplantar areas were heavily affected in the acute episodes (Fig. 1k), which led to considerable impairment in activities of daily living. Of note, palmoplantar involvement did not only affect the palmar and plantar areas, but also severely affected the acral areas of her fingers and toes. Correspondingly, nail changes (nail dystrophy) persisted and could be observed after resolution of a flare.

## 4 Conclusions

Generalized pustular psoriasis is a heterogeneous disease with a wide spectrum of disease severity and a highly variable clinical course. A clear understanding of the disease characteristics and clinical course of GPP has been hindered by the rarity of the disease and the lack of a universally accepted definition of a significant GPP flare. There is a need to develop an international consensus guideline for the definition of a GPP flare to enable the compilation and comparison of future studies on this rare disease. A better understanding of the severity spectrum and clinical course of GPP is needed to inform clinical practice.

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