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VIEWPOINT

Diversity in the clinical presentation of generalized pustular psoriasis (GPP): A series of case vignettes from around the world

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Abstract

A key principle of clinical studies and case reports is that they should reflect the demographics and epidemiology of the patient population concerned. Here, we have compiled a diverse group of clinical cases of generalized pustular psoriasis (GPP) to showcase the differences in GPP presentation in patients worldwide. We attempt to capture the broad spectrum of clinical presentations of GPP and showcase the diversity of the patient population. The patients included in this series are diverse in age, genetic background, skin phototype and medical history. Moreover, they present with a variety of clinical courses of GPP and different degrees of systemic involvement, and experience flares triggered by different inciting factors. The key learnings from this case series may support physicians in identifying and managing patients with this rare and multifaceted disease that can affect patients both physically and psychologically.

KEYWORDS
case study, generalized pustular psoriasis

1 | INTRODUCTION

Sicily Mburu, Peter van de Kerkhof

A key principle of clinical studies and case reports is that they should reflect the demographics and epidemiology of the patient population concerned. Despite this, information on dermatologic diseases continues to be inadequately representative. There is a need for greater diversity when reporting clinical cases,[1,2] with Caucasian patients often overrepresented in dermatology studies.[3,4] A greater awareness of the diverse clinical presentation of dermatologic diseases is needed to support improvements in the clinical evaluation of patients and to promote early, accurate diagnoses. Furthermore, understanding of the distinct presentations of dermatologic diseases across global populations and at different stages of life is needed to ensure that patients have access to effective treatment and equality of care. Here, we have compiled a diverse group of clinical cases of generalized pustular psoriasis (GPP) to showcase the differences in GPP presentation in patients worldwide.

The clinical presentation and course of GPP is highly heterogeneous, both between flares in an individual, and between patients.[5–7] GPP can present at any age and whereas some patients experience recurrent disease with periodic GPP flares, others have persistent mild pustular lesions with episodes of increased severity.[8,9] Moreover, flares may be associated with symptoms of systemic inflammation.[9,10] Skin inflammation can also cause systemic effects, especially when large areas of skin are involved.[11] A range of complications are associated with GPP, such as septic shock, cardiac failure, liver disease, acute respiratory distress syndrome (ARDS), acute renal failure and capillary leak syndrome.[12–15] This heterogeneity of GPP signs and symptoms presents a considerable barrier to accurate, early diagnosis.

In addition to the diversity of patients and heterogeneous clinical course of GPP, establishing a diagnosis is further complicated by the rarity of the disease. Dermatologists may have limited clinical experience with GPP, making the exclusion of differential diagnoses challenging.[16,17] There is also a paucity of literature describing the global spectrum of GPP. At this time of prevalent global travel and relocation, the chance of dermatologists seeing an unfamiliar GPP presentation is increased; thus an awareness of the variety of clinical presentations is crucial for reducing misdiagnoses.[17] Further complexity is added by the many different terms used to describe GPP and the lack of consensus regarding potential triggers. Although many different terms may be used to refer to GPP, they are all the same disease, for example, von Zumbusch type psoriasis; deficiency of the interleukin-36 receptor antagonist (DITRA); and impetigo herpetiformis (GPP of pregnancy).[18] Several inciting factors can trigger GPP flares in patients including stress[13]; pregnancy[19]; initiation/withdrawal of medications such as steroids and non-steroidal anti-inflammatories;[13,19,20] and infection (e.g., upper respiratory tract infections and staphylococcal or streptococcal infections).[21,22]

In our series of case reports, we attempt to capture the broad spectrum of clinical presentations of GPP and showcase the diversity of the patient population. The patients included in this series are diverse in age, genetic background, skin phototype and medical history. Moreover, they present with a variety of clinical courses of GPP and different degrees of systemic involvement, and experience flares triggered by different inciting factors. Overall, we hope that the key learnings from this case series may support physicians in identifying and managing patients with this rare and multifaceted disease that can affect patients both physically and psychologically.[19,23–25]

Key learnings

- DITRA is a form of GPP associated with *IL36RN* mutations
- Patients with *IL36RN* mutations present with GPP at a young age and have lifelong symptoms, which often include systemic inflammation
- Owing to the genetic heterogeneity of the disease, further evidence is required to establish genotype–phenotype correlations in GPP

2 | PATIENT 1: GPP IN INFANCY ASSOCIATED WITH GENETIC MUTATIONS

Lluís Puig

2.1 | Clinical summary

A female, neonatal patient developed widespread erythematous, desquamative plaques studded with pustules 2 months after being delivered by caesarean section at 34 weeks' gestation. Her skin lesions, initially localized to skin folds, rapidly became generalized (within 1 week) and tended to have an annular morphology with fine peripheral desquamation (Figure 1); she also presented with oral mucosa erosion. The patient required hospital admission twice; at the time of both hospital admissions, she was afebrile, had negative skin and blood cultures, and had leukocytosis with a white blood cell (WBC) count ranging between 16×10^9/L and 36×10^9/L. A skin biopsy revealed epidermal acanthosis with hypogranulosis, subcorneal collections of polymorphonuclear leukocytes and mild periadnexal mixed inflammatory infiltrate.

Genetic analysis identified a heterozygous mutation of the *CARD14* gene (c.956G > A [p.Arg319Gln]) and a heterozygous mutation of the *IL36RN* gene (c.227C > T [p.Pro76Leu]). These mutations were identified in the patient's father and mother, respectively, both of whom are healthy and asymptomatic. Both mutations are of uncertain significance according to the National Center for Biotechnology Information's ClinVar archive[26,27]; however, the specific *IL36RN* mutation has previously been reported in patients with GPP,[28,29] and

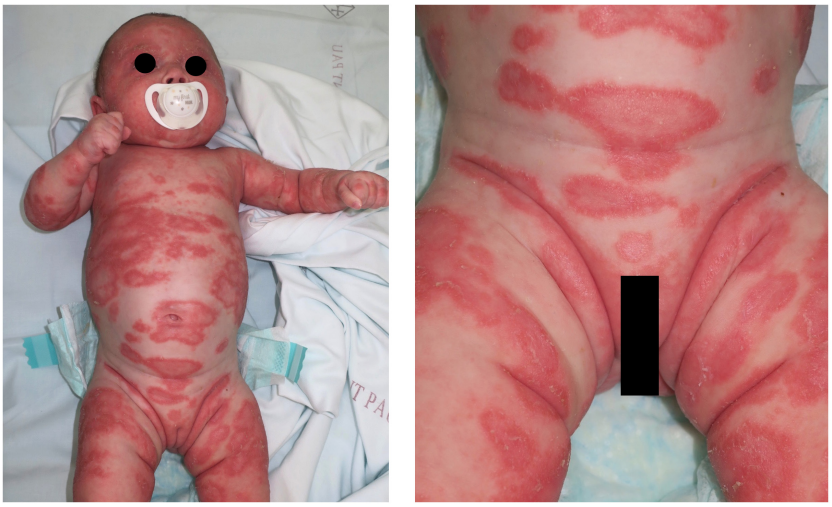

FIGURE 1 Patient's GPP lesions at 60 days old.

TABLE 1 Genetic mutations associated with GPP.

Mutation	Prevalence
IL36RN	21.0%–23.7% overall[31,32] 81.8% in patients without concomitant plaque psoriasis[33]
AP1S3	~10.8%[31]
MPO	5.3%[41]
CARD14	1.6%[31]

bioinformatic analyses and structural modelling predicted potential pathogenic effects.

2.2 | Discussion

Deficiency of the interleukin-36 receptor antagonist (IL-36Ra), or DITRA, is a genetic form of GPP that presents early in life and is associated with mutations in *IL36RN* (Table 1).[30] *IL36RN* mutations are present in 21%–24% of all patients with GPP, but the prevalence is higher in patients with GPP but without concomitant plaque psoriasis.[31–33] These *IL36RN* mutations result in a loss of function in IL-36Ra, uncontrolled IL-36 signalling and amplification of downstream inflammatory responses.[30] Patients with loss-of-function mutations in *IL36RN* have a distinct clinical phenotype of GPP, often presenting at an earlier age, and with a higher risk of systemic inflammation and higher recurrence rates than patients without mutations.[31,32,34–37]

In addition to an *IL36RN* mutation, the patient in this case also carried an alteration in *CARD14*, which has previously been identified in a small proportion of patients with GPP (Table 1). Although the precise pathogenesis of *CARD14* mutations is not fully understood, it has been suggested that gain-of-function alterations upregulate activity of the nuclear factor kappa B (NF-κB) in keratinocytes, leading to the development of psoriatic diseases.[38]

Studies suggest that the presence of co-occurring mutations or compound *IL36RN* mutations may affect the phenotypic presentation of GPP as well as response to treatment.[39,40] Affected patients with genetic mutations have lifelong GPP symptoms; therefore, identifying effective long-term therapeutic strategies is key to improving patient outcomes and minimising the impact of GPP on quality of life.

This case demonstrates the importance of recognising early signs and symptoms of GPP in neonatal patients and the need for long-term therapies for effective disease management as patients progress through childhood and into adulthood. Furthermore, this case report illustrates the genetic heterogeneity of GPP, which can make it difficult to determine genotype–phenotype correlations.

3 | PATIENT 2: CHALLENGES OF MANAGING GPP THROUGH LIFE TRANSITIONS

Ricardo Romiti

3.1 | Clinical summary

This 18-year-old woman was diagnosed with GPP shortly after birth and had experienced repeated outbreaks of skin pustules and oedema ever since. There was no family history of psoriasis or GPP and genetic testing was not available. Throughout the patient's childhood, GPP flares were associated with symptoms of systemic inflammation (malaise, asthenia and fever) and lasted for 2–3 weeks. At age 5 years (Figure 2A), the patient was started on a course of treatment with a retinoid, which resulted in disease remission for the following 5 years. At age 12 years, the decision was made to gradually reduce and then discontinue her treatment because of the drug's teratogenic adverse reactions, which make it unsuitable for women

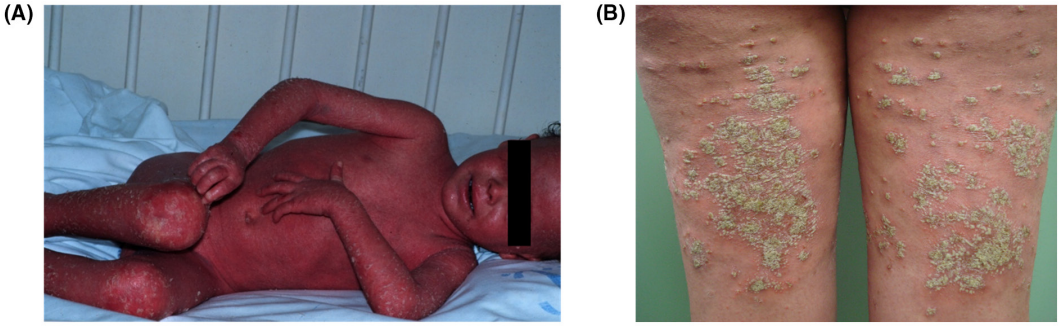

FIGURE 2 Lesions from the patient's GPP flares at (A) 5 years of age and (B) 18 years of age, which resulted in a fatal outcome.

of child-bearing age. She remained asymptomatic over the following 5 years but experienced a new GPP flare at 17 years of age that required admission to intensive care because of the development of pneumonia and septicaemia. Treatment with a tumour necrosis factor alpha (TNF-α) inhibitor was initiated, but after 45 days the patient presented with a further GPP flare with no apparent trigger factors (Figure 2B). TNF-α inhibitor treatment was continued; however, the patient developed sepsis with massive pulmonary involvement, ARDS, hepatitis and septic shock. Despite admission to the intensive care unit, the patient died 1 month after presenting with the GPP flare.

3.2 | Discussion

Childhood diagnosis of GPP is rare but accounts for up to 13% of childhood psoriasis.[42] In cases of GPP presenting in childhood, difficult clinical decisions may be needed to adapt treatment as the patient develops into an adult and during subsequent life events. Treating children is particularly challenging as there are limited data on GPP treatment in paediatric populations.[10] Furthermore, there is disagreement among experts over whether the use of systemic anti-inflammatory therapies is appropriate in children,[17] and guidelines by the Japanese Dermatological Association (JDA) note that young patients treated with retinoids need to be closely monitored for growth abnormalities and teratogenic adverse reactions.[10]

Throughout the patient's lifetime, healthcare professionals must re-evaluate treatment strategies to accommodate life milestones; for example, retinoid treatment was discontinued in this patient when she reached menarche. Physicians must balance the risks of pregnancy in the patient against the risk of teratogenicity with retinoid treatment, noting that the potential consequences of non-treatment may be higher. Currently, there are no guidelines on how treatment of paediatric GPP should evolve as patients progress through life.

It is important to note that, even in patients who are otherwise well managed, GPP flares are unpredictable and potentially life-threatening due to complications that can arise from systemic involvement, such as sepsis, heart failure and renal failure.[12,21] Each treatment decision is therefore associated with risks and should always be made in conjunction with patients and families.

Key learnings

- Flares are unpredictable and can be life-threatening, so long-term treatment is required
- Flares can present even after a period of successful treatment, so risk assessments should be performed when patients go through life changes that necessitate a treatment change
- Treatment decisions made during the transition from childhood to adulthood are often challenging and should involve the patient and family

4 | PATIENT 3: GPP IN PREGNANCY (IMPETIGO HERPETIFORMIS)

Siew Eng Choon

4.1 | Clinical summary

A 30-year-old Chinese woman with recurrent GPP was admitted to hospital while 33 weeks pregnant, with extensive pustulosis and lakes of pus (>90% affected body surface area [BSA]), including painful pustular lesions on her face, palms and soles (Figure 3). An emergency lower segment caesarean section was performed because of moderate meconium-stained liquor and decreased foetal movement. Although skin pustulation settled 2 weeks postpartum, the patient experienced persistent erythroderma with recurrent pustules on her lower limbs.

The patient first developed scalp lesions accompanied by a few painful pustular plaques on her legs at the age of 24. Over the course of the following 5 years the patient experienced pustular flares every 2–3 months, due to inadequate response to methotrexate, acitretin, cyclosporine and adalimumab. Her pregnancy triggered a progressive worsening of GPP symptoms, despite cyclosporine treatment,

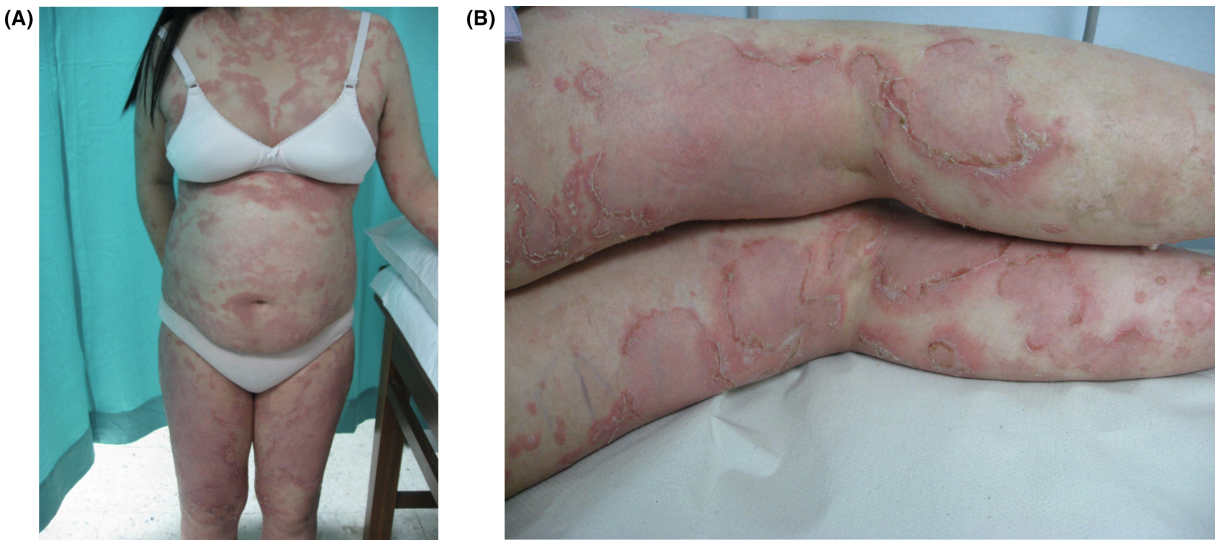

FIGURE 3 Patient's GPP lesions on (A) her body at 24 weeks of pregnancy and (B) her leg upon admission to hospital at 33 weeks' gestation.

which led to hospital admission at 33 weeks' gestation. Postpartum, her severe GPP did not respond to three doses of ustekinumab and settled only after combination treatment with methotrexate. While on acitretin maintenance, the patient typically experiences severe symptoms of GPP (≥60% BSA, severe pustulosis and leukocytosis of 13×10^9–17×10^9/L) for between 3 and 6 weeks at least three times a year. Triggers of her flares include upper respiratory tract infection, stress and menstruation.

4.2 | Discussion

GPP can be triggered and exacerbated by pregnancy[43–45] and typically presents in the third trimester; this form of GPP is often referred to as impetigo herpetiformis. The development of GPP in pregnancy presents a considerable clinical challenge and is associated with poor foetal outcomes (e.g., placental insufficiency, stillbirth, foetal abnormalities).[46] GPP can also become life-threatening to the mother if not effectively treated.

Effective clinical management requires close monitoring of the foetus and mother as well as therapeutic intervention with rapid onset of action. However, there is a paucity of evidence for effective treatments for GPP in pregnancy and no international consensus on the optimal therapeutic approach. The only guidelines that discuss GPP in pregnancy are those published by the JDA; they note that retinoids and methotrexate are contraindicated for pregnant patients, limiting the number of therapeutic options available.[10] Furthermore, many women experience recurring GPP in subsequent pregnancies.[46]

Overall, cases of GPP during pregnancy present a particular challenge for physicians, with a lack of guidance and treatment options for effective management. There remains a need to improve clinical outcomes for the mother and foetus.

Key learnings

- Pregnancy-induced GPP, also known as impetigo herpetiformis, is challenging to manage
- Close monitoring of the foetus and mother is vital to reduce the risk of poor outcomes for both the foetus and mother
- Effective and safe treatment options are needed to improve outcomes in pregnant women with GPP

5 | PATIENT 4: CHALLENGES OF DIAGNOSING GPP IN SKIN OF COLOUR

Boni E. Elewski

5.1 | Clinical summary

A 56-year-old woman with Fitzpatrick skin type V (rarely burns and tans easily)[47] was admitted to the intensive care unit (ICU) with a fever of 40°C, shaking chills, leukocytosis (WBC, 17×10^9/L) and low haemoglobin (9.8 g/dL). She presented to the ICU with widespread pustular lesions on an erythematous base involving most of her skin, including the palms, soles, trunk and extremities (Figure 4).

One week prior to presentation, she saw a community dermatologist for the skin eruption; she was subsequently diagnosed with psoriasis and treated with 0.1% triamcinolone cream. The rash worsened, and her condition deteriorated causing eventual admission to the ICU. The patient had a past history of high blood pressure and

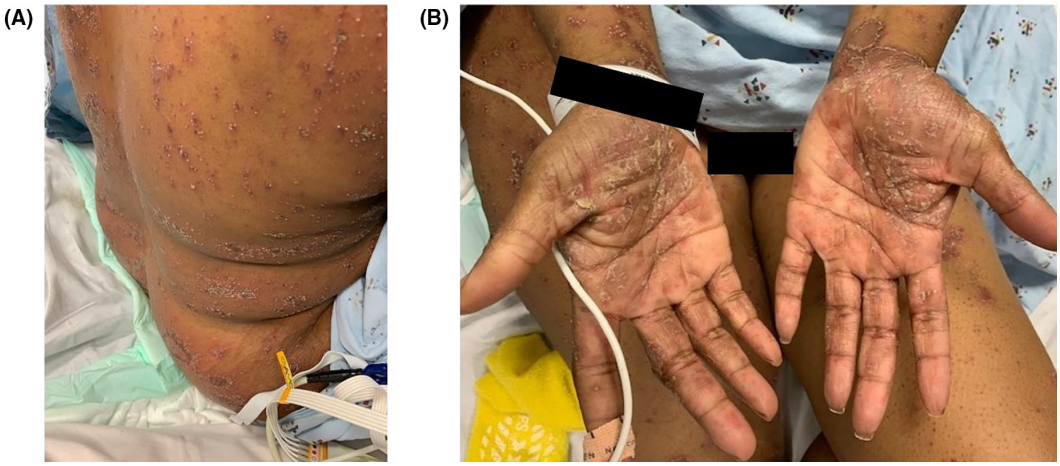

FIGURE 4 Pustular lesions on the patient's (A) trunk and (B) palms.

arrhythmia treated with metoprolol, the dosage of which had been increased 2–3 weeks before presentation at the hospital.

Upon admission to the ICU, she was diagnosed with sepsis and empiric treatment with vancomycin was initiated. However, blood cultures were negative. Dermatology was consulted and a complete body examination revealed annular pustules on her trunk, palms, soles, scalp and extremities associated with background erythema. A skin biopsy revealed subcorneal pustules, confirming the clinical suspicion of GPP.

GPP symptoms may have been precipitated by the escalating dosage of metoprolol. However, her condition was further complicated by the development of widespread linear immunoglobulin A (IgA) bullous disease, a rare autoimmune dermatosis that can be caused by vancomycin treatment. Her IgA bullous disease was managed with prednisone treatment.

5.2 | Discussion

At the time of writing, Caucasian patients are largely overrepresented in published case reports and clinical studies in patients with GPP.[3,4] It is particularly important to fully represent the diversity of patients with GPP as its clinical presentation may be influenced by patient ethnicity and skin type. Erythema, a hallmark of GPP and a key factor in assessing disease severity, may be more difficult to detect in patients with skin of colour, often presenting as a brown hue rather than the pink flush seen in patients with lighter skin. In this case, the patient was misdiagnosed twice, potentially because the skin erythema was difficult to detect due to her skin phototype, which was complicated further by inappropriate antibiotic treatment resulting in the development of IgA bullous dermatitis.

Owing to the rarity of GPP, there is a paucity of literature describing its presentation in patients of colour; however, studies in plaque psoriasis have shown that patient ethnicity may affect the extent of disease involvement and its impact on quality of life.[48] Achieving clear skin is also more challenging in skin of colour than in white skin, as patients are more likely to develop skin hyperpigmentation or hypopigmentation that may never resolve; physicians should consider and discuss these risks with patients. There is an important need for data describing the long-term effects of GPP on skin of colour.

Overall, this case demonstrates the challenges associated with diagnosing GPP in patients with more pigmented skin, and highlights the damaging consequences of misdiagnosis. A better understanding of the distinct presentations of GPP in a broad range of patients will support widespread improvements in the clinical evaluation of GPP and in achieving rapid and accurate GPP diagnoses.

Key learnings

- Features of GPP such as erythema may be difficult to detect in skin of colour, which might present a barrier to diagnosis
- Patients with skin of colour have an increased risk of hyperpigmentation and hypopigmentation after lesions resolve
- Greater understanding of the heterogeneity in GPP presentation will support more rapid and accurate diagnosis in a diverse range of patients

6 | PATIENT 5: POTENTIAL TRIGGERS AND ACUTE COMPLICATIONS OF GPP

Marina Venturini

6.1 | Clinical summary

A 60-year-old woman presented with superficial pustules arising on erythematous patches and erythematous, desquamative plaques (Figure 5).

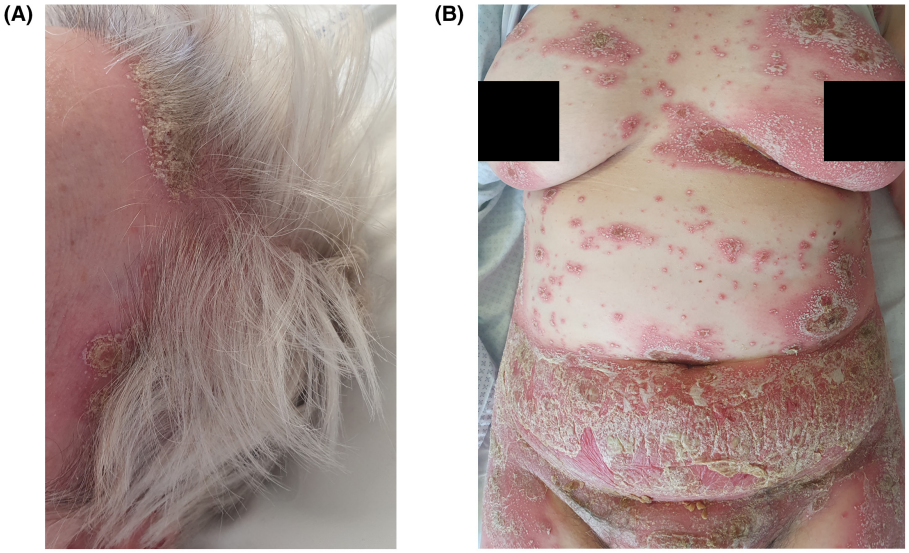

FIGURE 5 GPP lesions on the patient's (A) scalp and (B) body.

She reported symptoms of asthenia and a burning sensation from her skin lesions, and she had a fever of 38°C. Laboratory findings revealed that the patient had leukocytosis (WBC, 13.8 $\times 10^3/\mu L$), hypocalcaemia (total calcium, 5.17 mg/dL) and elevated levels of C-reactive protein (CRP; 296 mg/L), aspartate aminotransferase (90 U/L) and alanine transaminase (121 U/L). Based on these findings, the patient was diagnosed with GPP, which was supported by biopsy results showing subcorneal and intraepidermal pustular dermatitis. The patient was treated with systemic corticosteroids (methylprednisolone 0.5 mg/kg) as well as calcium and vitamin D supplements. She was discharged 21 days after the onset of GPP symptoms. However, 1 week later, she presented at the emergency room with worsening asthenia and postural instability and was admitted to the nephrology unit for acute renal failure (severe hypercalcemia and hyperkalaemia); she was discharged 11 days later. After another week, she was readmitted to hospital with hypercalcemia, appearance of new pustular lesions and symptoms of systemic inflammation, including fever.

The patient had a family history of psoriasis on her mother's side, and she had experienced plaque psoriasis limited to the scalp from the age of 30. The patient had undergone a total thyroidectomy because of a multinodular goitre at the age of 33 but had never received vitamin D/calcium supplements. Severe hypocalcaemia due to post-surgical, untreated hypoparathyroidism was therefore identified as a possible triggering factor for the patient's GPP flare.

6.2 | Discussion

GPP flares can be triggered by a variety of inciting factors. In this case, we report a patient with a GPP flare triggered by hypocalcaemia due to hypoparathyroidism following a total thyroidectomy 27 years prior. Other commonly reported triggers of GPP include stress, infection and the initiation or withdrawal of corticosteroids.[13,20,21] Hypocalcaemia has previously been reported as a trigger of GPP in several case reports, frequently secondary to hypoparathyroidism.[49–53] However, in this case, it is unclear why the patient developed GPP almost three decades after her thyroidectomy; this suggests an interaction with other triggering factors, such as the stress-induced modulation of calcium levels. Although the exact mechanism has not been elucidated, the roles of calcium and vitamin D in cell–cell adhesion and skin cell proliferation, respectively, may contribute to the link between hypocalcaemia and GPP.[49,53]

Systemic inflammation associated with GPP flares can lead to severe, life-threatening conditions, including ARDS and congestive heart failure. The patient reported here was re-admitted to hospital for acute renal failure, another common complication associated with systemic inflammation in GPP, 1 week after being discharged.[54–57] The clinical management of patients with acute renal failure requires a multidisciplinary approach, and treatment should aim to rapidly resolve nephrological symptoms and avoid other systemic complications. It is also important for physicians to consider that some treatments commonly used to treat GPP (e.g., retinoids and cyclosporine) may complicate pre-existing renal conditions and, therefore, may be contraindicated in patients with renal complications.[10]

Overall, this case demonstrates the potentially life-threatening and unpredictable course of GPP flares and highlights GPP as a systemic inflammatory illness requiring a multidisciplinary approach to treatment.

Key learnings

- GPP flares can be triggered by several factors, including hypocalcaemia resulting from post-surgical hypoparathyroidism
- Flares can become life-threatening due to complications such as acute renal failure, which can develop when systemic inflammation is not effectively managed

7 | PATIENT 6: MULTIDISCIPLINARY MANAGEMENT OF AN ADULT CASE OF GPP WITH COMORBIDITIES

Songmei Geng

7.1 | Clinical summary

A 64-year-old woman was referred by her dermatologist 6 months after first presenting with symptoms of GPP; she had originally been diagnosed with subcorneal pustular dermatosis and had no prior history of pustular psoriasis. She had several comorbidities, including type 2 diabetes, hypertension (very high risk), coronary artery disease, incomplete right bundle branch block, hypoproteinaemia and hypokalaemia, and had previously had a hysterectomy.

The patient presented with 70% BSA affected and a Generalized Pustular Psoriasis Physician Global Assessment score of 3 (Figure 6). Her level of self-reported pain as per the pain visual analog scale was 4/10. Laboratory findings at the time of hospitalization revealed leukocytosis (WBC, 19.8×10^9/L), elevated levels of CRP (29.4 mg/L) and a bilirubin level of 8.0 μmol/L. Owing to the patient's many comorbidities and long history of substantial glucocorticoid use, it was important to closely monitor her blood glucose levels and blood pressure during treatment and prevent adverse reactions associated with glucocorticoid use and the potential for disease rebound after dose reduction. A multidisciplinary approach was taken, with cardiovascular physicians and endocrinologists consulted to ensure optimal management of the patient's several conditions.

7.2 | Discussion

Although the mean age of onset is between 41 and 58 years, GPP can also present in older patients with no previous history.[58] Prognosis is particularly poor in elderly patients, due to the development of systemic complications such as infection, sepsis or cardiorespiratory failure.[58,59] Moreover, the occurrence of comorbidities is higher in patients with GPP compared with the general population and also compared with patients with plaque psoriasis.[60] The comorbidities presented in this case report (hypertension, obesity and type 2 diabetes) are among those most frequently identified in patients with GPP.[61,62]

The presence of comorbidities exacerbates the risks associated with GPP flares; patients are more likely to develop life-threatening complications such as congestive heart failure, acute renal failure and sepsis.[9] Comorbid conditions also increase the impact on quality of life, with patients commonly reporting feelings of depression and anxiety.[24,61]

When managing patients with GPP and multiple comorbidities, a long-term, multidisciplinary approach is required to ensure that all aspects of the patient's needs are considered and appropriate treatment decisions taken; many of the available treatments are associated with adverse reactions that could become serious in patients with systemic inflammation and underlying diseases.

Key learnings

- GPP can present in adults of advanced age with no prior history of the disease
- The presence of comorbidities, including hypertension and type 2 diabetes, increases the risk of developing life-threatening complications during a GPP flare
- A multidisciplinary approach is required to address all aspects of the patient's needs

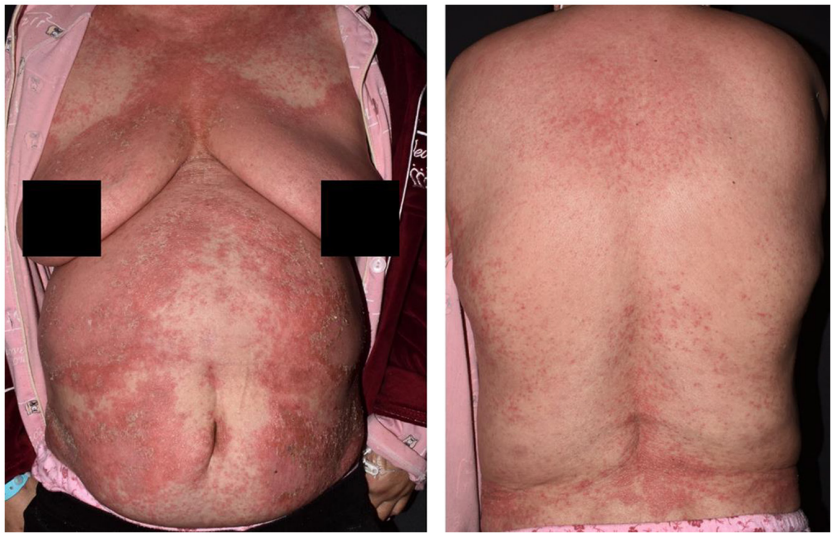

FIGURE 6 Patient's GPP lesions upon admission to hospital.

8 | PATIENT 7: A CASE OF GPP ASSOCIATED WITH SYSTEMIC INFLAMMATION AND MULTIPLE COMORBIDITIES

Hideki Fujita

8.1 | Clinical summary

A 67-year-old man presented with erythema and pustules covering 70% BSA, which had appeared 1 week prior (Figure 7A). He also experienced pain, scaling and a burning sensation, as well as symptoms of systemic inflammation such as fever, malaise, fatigue and oedema. The patient had a JDA GPP severity index score of 12/17, indicating severe disease. He had no family history of GPP and no previous history of similar symptoms. A skin biopsy revealed acanthosis and Kogoj's spongiform pustules (Figure 7B). These histological findings confirmed a diagnosis of GPP, as per JDA diagnostic criteria (Table 2). Laboratory tests revealed leukocytosis (WBC, 13.9×10^9/L), neutrophilia (83.5% neutrophils), elevated CRP levels (119.0 mg/L) and high creatinine (2.7 mg/dL). In addition to symptoms of systemic inflammation, the patient also presented with acute renal dysfunction, as indicated by his elevated creatinine levels.

The patient had several comorbidities affecting his overall health, including hypertension, plaque psoriasis, psoriatic arthritis, chronic kidney disease and dyslipidaemia. Consequently, a multidisciplinary approach was necessary for disease management; he was referred to a cardiologist to manage hypertension and dyslipidaemia, a rheumatologist for psoriatic arthritis and a nephrologist for kidney disease. In follow-up appointments, the patient reported recurrent disease flares.

8.2 | Discussion

GPP skin lesions are painful, debilitating and have a considerable impact on patients' quality of life; effective management of the systemic symptoms that can accompany a GPP flare is also needed to prevent the development of life-threatening complications. In this case, the patient's first GPP flare was accompanied by oedema, fever and malaise, as well as leukocytosis, high creatinine, neutrophilia and elevated levels of CRP. The patient was assessed as having severe disease according to the JDA severity index, which is the only clinical outcome measure for GPP that considers systemic symptoms in the score calculation.[6,63] Of note, oedema is a sign of capillary leak syndrome and may indicate that a patient is at high risk of developing cardiac failure, ARDS or renal insufficiency.[64] Given that cardiovascular impairment is a leading cause of mortality in GPP, area of oedema is a component of the JDA severity index for assessing GPP severity. Here, the patient's JDA severity index score of 12/17 indicated that he was at high risk of medical emergency. It is crucial that physicians recognize patients with GPP at high risk of developing life-threatening complications. To this end, the JDA severity index is a useful tool for identifying patients with potentially life-threatening disease.

This case also highlights the importance of using a combination of symptoms, laboratory findings and histological analysis to guide a diagnosis of GPP. Although this patient's signs and symptoms were

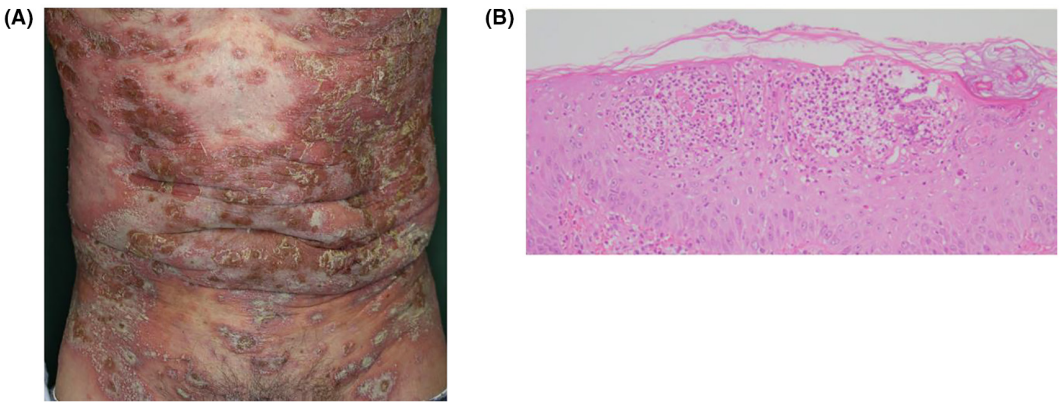

FIGURE 7 (A) Pustular lesions on the patient's trunk, and (B) skin biopsy showing hallmark histological features of GPP.

TABLE 2 Primary criteria for a diagnosis of GPP, as per JDA guidelines.[10]

Primary parameters	
1.	Systemic symptoms such as fever and fatigue
2.	Systemic or extensive flush accompanied by multiple sterile pustules that sometimes merge to form lakes of pus
3.	Neutrophilic subcorneal pustules histopathologically characterized by Kogoj's spongiform pustules
4.	The above clinical and histological features recur repeatedly

indicative of a GPP diagnosis, it was confirmed by histological findings showing hallmark features of GPP such as Kogoj's spongiform pustules. Histological findings are required for a GPP diagnosis according to JDA guidelines, but are not a requirement in ERASPEN guidelines, though they can be used to support a diagnosis.[8,10]

Key learnings

- Patients with GPP who experience systemic symptoms, such as oedema and fever, are more likely to develop life-threatening complications
- The JDA severity index considers systemic symptoms when assessing GPP severity, and is a useful tool for identifying patients at high risk of medical urgency
- Standardized, global diagnostic criteria will support physicians in making rapid GPP diagnoses and improve clinical outcomes

AUTHOR CONTRIBUTIONS

Siew Eng Choon, Boni E. Elewski, Hideki Fujita, Songmei Geng, Lluís Puig, Ricardo Romiti and Marina Venturini provided clinical information for their respective patients. All authors participated in the drafting and review of the manuscript. All authors have read and approved the final manuscript and controlled the decision to submit.

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SEC declares paid activities as an advisor, speaker or consultant for AbbVie, Boehringer Ingelheim, Eli Lilly, Janssen, LEO Pharma, MSD, Novartis, Pfizer, Sanofi and UCB. BE is an investigator for AbbVie, Amgen (previously Celgene), AnaptysBio, Bausch Health (formerly Valeant Pharmaceuticals), Boehringer Ingelheim, Bristol Myers Squibb, Eli Lilly, Incyte, LEO Pharma, Menlo, Merck, Novartis, Pfizer, Regeneron, Sun Pharmaceutical Industries, UCB and Vanda; and is a consultant for Amgen (previously Celgene), Arcutis, Bausch Health (formerly Valeant Pharmaceuticals), Boehringer Ingelheim, Bristol Myers Squibb, Eli Lilly, LEO Pharma, Novartis and UCB. HF declares receiving honoraria or fees for serving on advisory boards, as a speaker, and as a consultant, as well as grants as an investigator, from AbbVie, Amgen, Boehringer Ingelheim, Bristol Myers Squibb, Daiichi-Sankyo, Eisai, Eli Lilly, Janssen Pharmaceuticals, Japan Blood Products Organization, JMEC, Kaken, Kyowa Kirin, LEO Pharma, Maruho, Mitsubishi Tanabe Pharma, Nihon Pharmaceutical, Novartis, Otsuka Pharmaceutical, Sanofi, Sato Pharmaceutical, Sun Pharmaceutical Industries, Taiho Pharmaceutical, Torii Pharmaceutical, UCB and Ushio. SG has no conflict of interest to disclose. PvdK received fees for consultancy service or lectureships from AbbVie, Almirall, Amgen, Boehringer Ingelheim, Bristol Myers Squibb, Dermavant Sciences, Eli Lilly, Janssen, LEO Pharma, Novartis and UCB. SM has not received individual compensation, however, on behalf of the IFPA, has received fees for consultancy services and/or lectureships from Almirall, Boehringer Ingelheim, Novartis and UCB. In the past 12 months, the IFPA has accepted grants and funding from AbbVie, Almirall, Amgen, Bristol Myers Squibb, Boehringer Ingelheim, Eli Lilly, Janssen, Leo Pharma, Novartis, Pfizer and UCB. LP has received consultancy/speaker's honoraria from and/or participated in clinical trials sponsored by AbbVie, Almirall, Amgen, Biogen, Boehringer Ingelheim, Bristol Myers Squibb, Eli Lilly, Janssen, LEO Pharma, Novartis, Pfizer, Sandoz, Sanofi and UCB. RR declares receiving honoraria as a scientific consultant, speaker or clinical study investigator for AbbVie, Boehringer Ingelheim, Galderma, Janssen-Cilag, Eli Lilly, LEO Pharma, Novartis, Pfizer, Pierre-Fabre, Sanofi, Teva and UCB. MV has received consultancy fees or lectureships from AbbVie, Almirall, Amgen, Eli Lilly, Galderma, LEO Pharma, Novartis, Pierre Fabre and UCB.

CONSENT STATEMENT

All patients in this case series provided informed consent for their photographs to be used in medical publications.

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