REVIEW ARTICLE

Diagnosis of Generalized Pustular Psoriasis

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Abstract

Generalized pustular psoriasis (GPP) is a severe rare skin disease characterized by widespread eruption of sterile superficial macroscopic pustules with or without systemic inflammation. Generalized pustular psoriasis flares may lead to life-threatening multiorgan complications, which highlights the need for rapid and accurate diagnosis. However, the rarity of the disease and its heterogeneous cutaneous and extracutaneous symptoms, and the resemblance of symptoms to other skin conditions, pose considerable challenges to the timely diagnosis and treatment of patients with GPP. Current laboratory tests used for GPP diagnosis are generally not GPP specific, and are mainly focused on the assessment of inflammatory markers and clinical and histopathologic features of GPP, and emerging genetic screening approaches. A differential diagnosis to distinguish GPP from other similar conditions requires careful assessment of the patient's skin symptoms, potential disease triggers, medical history, histopathologic features, laboratory tests, and clinical disease course. The comprehensive interpretation of these assessments can be challenging owing to the lack of standardized global guidelines. While there is currently a lack of standardized international guidelines for the diagnosis of GPP, recent advances in our understanding of the genetics and pathogenesis of the disease have provided new opportunities to enhance diagnosis. In the future, defining specific GPP subtypes using genetic and histopathologic strategies will guide therapeutic decisions, allowing patients to achieve their treatment goals without delay. In this article, we provide an overview of the current diagnostic methods, differential diagnostic strategies, and future advances in the diagnosis of GPP, as well as features of GPP variants.

Key Points

Generalized pustular psoriasis is a severe rare skin disease that has a considerable effect on patient quality of life and can be life threatening if disease flares are not diagnosed accurately and treated promptly.

Differential diagnosis of generalized pustular psoriasis requires careful interpretation of a patient's laboratory tests, clinical and histopathologic features, and medical history to exclude other inflammatory skin conditions.

There is a need to develop standardized international guidelines to improve the diagnosis and treatment of patients with generalized pustular psoriasis and rapidly exclude other skin conditions that require different treatment strategies.

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1 Introduction

Generalized pustular psoriasis (GPP) is a severe rare skin disease characterized by widespread eruptions of sterile pustules with or without systemic inflammation [1]. Because of the extracutaneous manifestations of the disease, which include fever, leukocytosis, general malaise, and may include multiorgan involvement, GPP flares can be life threatening if not diagnosed accurately and treated promptly [2]. However, there is a lack of international consensus on the diagnosis and management of patients with GPP, and the rarity of the disease and absence of consistent diagnostic criteria and methodologies are substantial hurdles to achieving an accurate diagnosis [3, 4]. Although there are similarities among the available guidelines [1, 5], recent advances in our understanding of the pathogenesis of GPP offer new opportunities to develop internationally standardized guidelines and adopt new methodologies for accurate and rapid diagnosis of the disease. In this article, we highlight the clinical spectrum of GPP and the diagnostic challenges due to the lack of standardized guidelines, provide an overview of the current methods for the diagnosis of GPP, and describe the available differential diagnostic strategies.

2 Clinical Diagnosis of GPP

Generalized pustular psoriasis is most common during the fourth decade of life and more prevalent in female than male individuals [6]. Patients with GPP typically present with a rapid onset of widespread pustules on ill-defined areas of erythema and edema [6, 7]. According to the Japanese guidelines, GPP is diagnosed based on the repeated recurrence of systemic symptoms, such as fever and fatigue, extensive flushing accompanied by the eruption of multiple sterile pustules that can merge to form "lakes of pus", and the presence of Kogoj's spongiform pustules [5]. The severity of GPP is categorized as mild, moderate, or severe based on the total score of skin signs, which includes a rating of erythema, pustules, and edema in combination with a systemic inflammation score of fever, white blood cell count, and serum C-reactive protein and albumin levels [5]. Based on a recent international consensus by the European Rare and Severe Psoriasis Expert Network (ERASPEN), GPP is defined as primary sterile visible pustules on non-acral skin and can be subclassified into GPP with or without systemic inflammation and with or without plaque psoriasis [1]. In addition, the disease course can be relapsing or persistent [1]. A complete physical examination of the skin and mucosae is mandatory to evaluate the extent of involvement [6]. The mucosal examination findings typically include a geographic or fissured tongue, cheilitis, and ocular involvement (e.g., conjunctivitis, uveitis, and iritis). In addition, the cutaneous symptoms associated with GPP flares may include pain, burning, and pruritus. Because of the systemic nature of the disease, extracutaneous manifestations may include nail abnormalities, arthralgia, jaundice, and edema of the lower extremity [6].

History of concurrent or previous plaque psoriasis is helpful for confirming a GPP diagnosis; however, not all patients with GPP have a history of plaque psoriasis [6, 8]. In addition, potential triggers of GPP flares, which may include medications, infections, stress, and pregnancy, should be investigated [2, 8–10]. As several patterns of medication use have been found to trigger GPP flares, a complete medication history should be explored. For example, GPP flares can be triggered by rapid tapering or sudden withdrawal of systemic corticosteroids or cyclosporine, drugs such as amoxicillin and terbinafine, or ointments including calcipotriol and betamethasone [11–14]. Paradoxical eruption of GPP flares has also been reported with the use of tumor necrosis factor-α inhibitors and ustekinumab [15–17]. However, differential diagnosis of medication-induced GPP flares vs acute generalized exanthematous pustulosis (AGEP) represents a clinical challenge that requires careful clinical and laboratory assessments. Recent reports indicate that GPP can also be triggered by certain vaccines [18]. For example,

several recent case studies have shown a possible induction of GPP flares following the administration of vaccines for severe acute respiratory syndrome coronavirus 2, possibly through the induction of cytokines involved in the pathogenesis of GPP flares [19, 20]. Moreover, during the global COVID-19 pandemic caused by severe acute respiratory syndrome coronavirus 2, there were reports of cases of GPP exacerbation and evolution of acrodermatitis continua of Hallopeau into GPP following COVID-19 infection [21, 22].

Several infections have been linked to GPP flares, including streptococcal, *Trichophyton rubrum*, cytomegalovirus, Epstein–Barr virus, and varicella zoster virus [6]. Generalized pustular psoriasis can also be triggered by certain medical conditions, such as hypocalcemia, which can be caused by hypoparathyroidism [6, 23]. Pregnancy has also been reported to trigger a rare, potentially life-threatening variant of GPP known as impetigo herpetiformis. This form of GPP usually occurs during the third trimester and may recur during subsequent pregnancies (see Sect. 7.2) [24].

3 Current Laboratory Tests for the Diagnosis of GPP

Laboratory tests are needed to confirm a GPP diagnosis and to assess the level of systemic inflammation and possible systemic complications of the disease [6]. These tests are summarized in Table 1 [6, 25]. A potassium hydroxide test can also be performed to exclude other causes of scaling and pustulosis, such as generalized *tinea corporis* and disseminated candidiasis [26, 27].

4 Histopathologic Features of GPP

Skin biopsies may be performed to confirm a diagnosis of GPP [6, 28]. A key distinct histopathologic feature of GPP is the presence of Kogoj's spongiform pustules, which form due to the accumulation of neutrophils beneath the stratum corneum. Other features include parakeratosis, acanthosis, hyperkeratosis, elongated rete ridges, diminished stratum granulosum, and capillary dilation of the papillary dermis. Munro's microabscesses and superficial perivascular mononuclear cell infiltrations can also be observed [6].

5 Genetic Screening in GPP Diagnosis

Although genetic tests are not yet routinely used to confirm a GPP diagnosis, the future implementation of genetic screening may offer the opportunity to identify certain forms of GPP and personalize treatment strategies. Increased knowledge of genetic variants involved in the pathogenesis of GPP

and other pustular skin diseases will pave the way for the adoption of genetic screens in patient care. Among the most notable recent findings is the identification of *IL36RN* variants in patients with GPP and is seen in approximately 24% of patients with GPP [29]. Genotype–phenotype studies have shown that variants in *IL36RN,* encoding the interleukin-36 receptor antagonist, are associated with an earlier age of GPP onset and widespread inflammation, and are reported not to be related to concurrent or prior plaque psoriasis [7, 30]. *IL36RN* variants that result in interleukin-36 receptor antagonist deficiency are associated with severe forms of GPP and AGEP, another pustular skin disease triggered mainly by medications [31]. The breakthrough discovery of *IL36RN* variants in the pathogenesis of GPP led to the identification of a new form of GPP termed deficiency of the interleukin-36 receptor antagonist (DITRA) [32]. Variants in *CARD14*, which encodes a keratinocyte adaptor protein, were also identified in patients with GPP. The *CARD14* p. Asp176His gain-of-function variant was identified as a predisposing factor for GPP with plaque psoriasis; however, this variant was not associated with GPP alone in a Japanese population [30]. Variants in *AP1S3*, which encodes a subunit of the adaptor protein 1 complex, were also identified in patients with pustular psoriasis of European origin [33]. Most recently, *MPO* loss-of-function variants were discovered in patients with GPP; *MPO* variants cause an increase in neutrophil accumulation and activity [34]. In addition, a rare loss-of-function variant in *SERPINA3*, which encodes serine protease inhibitor A3 (serpin A3) that inhibits several proteases, was identified in patients with GPP; specifically, the heterozygous deletion c.966delT/p.Tyr322Ter in two patients with GPP was confirmed by Sanger sequencing. This rare variant was found to be associated with GPP and may impact the inhibitory effect of serpin A3 on cathepsin G [35].

6 Mixed Clinical Features and Differential Diagnosis

As several pustular skin conditions present with similar clinical features and symptoms, GPP requires effective differential diagnostic strategies (Fig. 1) [6, 25, 31, 36–41]. Below, we summarize two key differential diagnoses.

6.1 Acute Generalized Exanthematous Pustulosis

Acute generalized exanthematous pustulosis is a severe, acute, pustular skin reaction most often triggered by medications, and can present with fever, neutropenia, and peripheral blood eosinophilia [31]. Acute generalized exanthematous pustulosis pustules vary in size and are distributed over several epidermal levels of the skin [31]. Mucosal involvement has been reported in 20–25% of patients [36]. In AGEP, the subcorneal pustules are markedly spongiform and less prominent than GPP pustules. A skin biopsy can further differentiate AGEP from GPP based on the localization and spongiform characteristic of the pustules. In addition, necrotic keratinocytes are more prevalent in AGEP than GPP; GPP pustules do not usually contain eosinophils and generally have more lysed keratinocytes and are localized at a slightly higher epidermal level than AGEP pustules [31]. The pustular eruptions usually affect the intertriginous areas [42], as demonstrated by a case of a pregnant woman who experienced numerous non-follicular pustules on her neck, axilla, wrist, and trunk triggered by the administration of ampicillin/cloxacillin sodium [43]. The prognosis of patients with AGEP is usually favorable; cutaneous symptoms typically resolve within 15 days of discontinuation of the causative agent [44].

Table 1 Laboratory tests and findings for the diagnosis of GPP and potential systemic complications [6]

Laboratory test	Findings in patients with GPP	Systemic complications
Complete blood cell count	Leukocytosis, lymphopenia [6, 25]	Systemic inflammation
Erythrocyte sedimentation rate	Elevated [6, 25]	
C-reactive protein	Elevated [6, 25]	
Plasma globulins (IgG or IgA)	Elevated [25]	
Blood chemistries	Hypoproteinemia and hypocalcemia [25]	Loss of plasma proteins into tissues
	Elevated blood urea nitrogen and creatinine [25]	Oligemia
	Elevated liver function enzymes (aspartate transaminase, alanine transaminase) [25]	Liver damage
Urinalysis	Positive for albumin [25]	Kidney damage
Bacterial culture of pustules and/or blood	Positive bacterial cultures [25]	Secondary bacterial infection

GPP generalized pustular psoriasis, *Ig* immunoglobulin

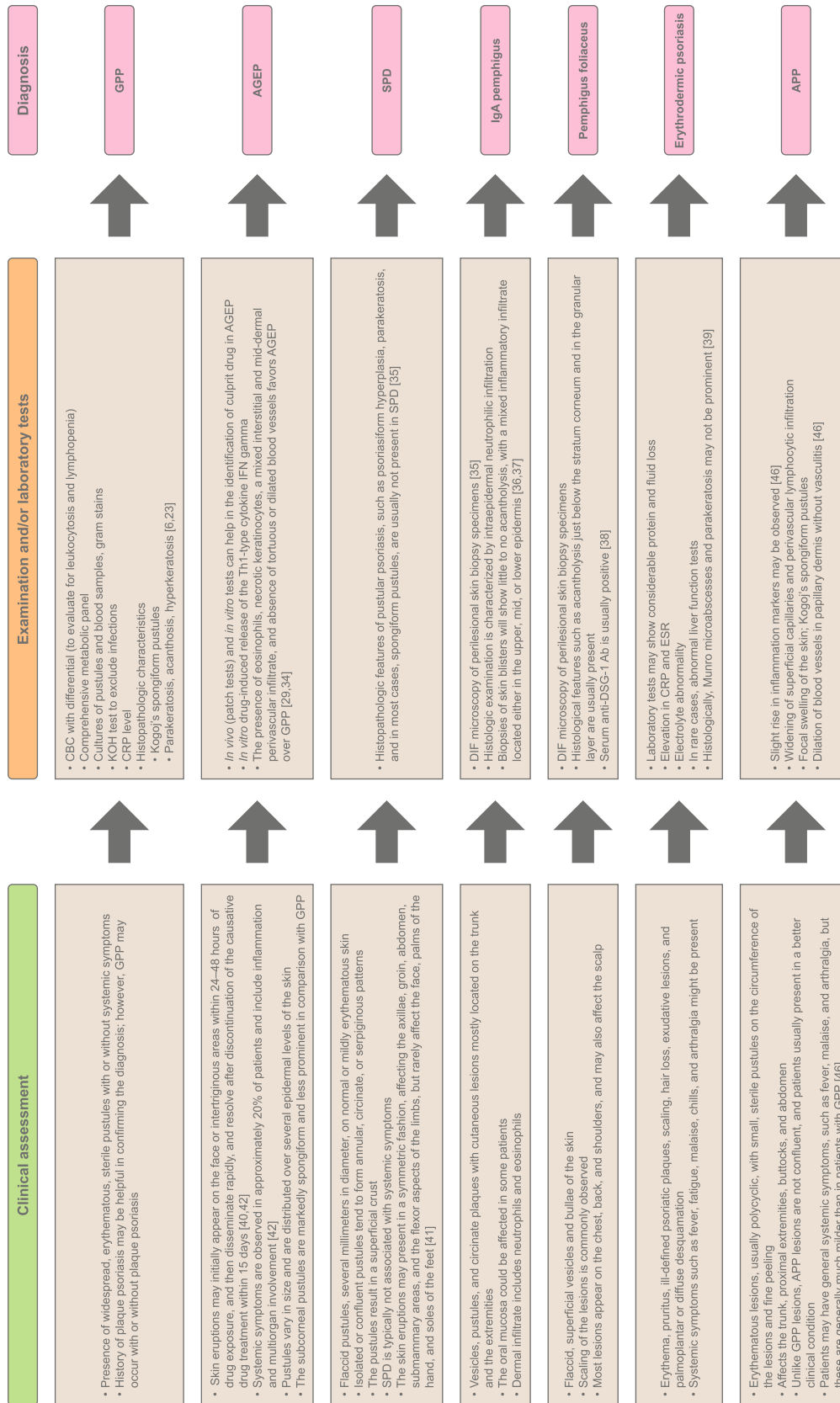| Clinical assessment	Examination and/or laboratory tests	Diagnosis

• Presence of widespread, erythematous, sterile pustules with or without systemic symptoms
• History of plaque psoriasis may be helpful in confirming the diagnosis; however, GPP may occur with or without plaque psoriasis
	• CBC with differential (to evaluate for leukocytosis and lymphopenia)
	• Comprehensive metabolic panel
	• Cultures of pustules and blood samples, gram stains
	• KOH test to exclude infections
	• CRP level
	• Histopathologic characteristics
	  • Kogoj's spongiform pustules
	  • Parakeratosis, acanthosis, hyperkeratosis [6,23]
		GPP

• Skin eruptions may initially appear on the face or intertriginous areas within 24–48 hours of drug exposure, and then disseminate rapidly, and resolve after discontinuation of the causative drug treatment within 15 days [40,42] • Systemic symptoms are observed in approximately 20% of patients and include inflammation and multiorgan involvement [42] • Pustules vary in size and are distributed over several epidermal levels of the skin • The subcorneal pustules are markedly spongiform and less prominent in comparison with GPP	• In vivo (patch tests) and in vitro tests can help in the identification of culprit drug in AGEP • In vitro drug-induced release of the Th1-type cytokine IFN gamma • The presence of eosinophils, necrotic keratinocytes, a mixed interstitial and mid-dermal perivascular infiltrate, and absence of tortuous or dilated blood vessels favors AGEP over GPP [29,34]	AGEP
• Flaccid pustules, several millimeters in diameter, on normal or mildly erythematous skin • Isolated or confluent pustules tend to form annular, circinate, or serpiginous patterns • The pustules result in a superficial crust • SPD is typically not associated with systemic symptoms • The skin eruptions may present in a symmetric fashion, affecting the axillae, groin, abdomen, submammary areas, and the flexor aspects of the limbs, but rarely affect the face, palms of the hand, and soles of the feet [41]	• Histopathologic features of pustular psoriasis, such as psoriasiform hyperplasia, parakeratosis, and in most cases, spongiform pustules, are usually not present in SPD [35]	SPD
• Vesicles, pustules, and circinate plaques with cutaneous lesions mostly located on the trunk and the extremities • The oral mucosa could be affected in some patients • Dermal infiltrate includes neutrophils and eosinophils	• DIF microscopy of perilesional skin biopsy specimens [35] • Histologic examination is characterized by intraepidermal neutrophilic infiltration • Biopsies of skin blisters will show little to no acantholysis, with a mixed inflammatory infiltrate located either in the upper, mid, or lower epidermis [36,37]	IgA pemphigus
• Flaccid, superficial vesicles and bullae of the skin • Scaling of the lesions is commonly observed • Most lesions appear on the chest, back, and shoulders, and may also affect the scalp	• DIF microscopy of perilesional skin biopsy specimens • Histological features such as acantholysis just below the stratum corneum and in the granular layer are usually present • Serum anti-DSG-1 Ab is usually positive [38]	Pemphigus foliaceus
• Erythema, pruritus, ill-defined psoriatic plaques, scaling, hair loss, exudative lesions, and palmoplantar or diffuse desquamation • Systemic symptoms such as fever, fatigue, malaise, chills, and arthralgia might be present	• Laboratory tests may show considerable protein and fluid loss • Elevation in CRP and ESR • Electrolyte abnormality • In rare cases, abnormal liver function tests • Histologically, Munro microabscesses and parakeratosis may not be prominent [39]	Erythrodermic psoriasis
• Erythematous lesions, usually polycyclic, with small, sterile pustules on the circumference of the lesions and fine peeling • Affects the trunk, proximal extremities, buttocks, and abdomen • Unlike GPP lesions, APP lesions are not confluent, and patients usually present in a better clinical condition • Patients may have general systemic symptoms, such as fever, malaise, and arthralgia, but these are generally much milder than in patients with GPP [46]	• Slight rise in inflammation markers may be observed [46] • Widening of superficial capillaries and perivascular lymphocytic infiltration • Focal swelling of the skin; Kogoj's spongiform pustules • Dilation of blood vessels in papillary dermis without vasculitis [46]	APP

Fig. 1 Differential diagnosis of generalized pustular psoriasis (GPP). *Ab* antibody, *AGEP* acute generalized exanthematous pustulosis, *APP* annular pustular psoriasis, *CBC* complete blood cell count, *CRP* C-reactive protein, *DIF* direct immunofluorescence, *DSG-3* desmoglein 3, *ESR* erythrocyte sedimentation rate, *IFN* interferon, *IgA* immunoglobulin A, *KOH* potassium hydroxide, *SPD* subcorneal pustular dermatosis, *Th1* helper T cell

6.2 Subcorneal Pustular Dermatosis

Subcorneal pustular dermatosis, also known as Sneddon–Wilkinson disease, is a rare relapsing eruption of sterile pustules of unknown etiology that develops most commonly in middle-aged or elderly female individuals [37]. Subcorneal pustular dermatosis presents with many flaccid pustules, several millimeters in diameter, on normal or mildly erythematous skin. Isolated or confluent pustules tend to form annular, circinate, or serpiginous patterns; however, they are characterized by unique topography compared with pustular psoriasis. The skin eruptions may present in a symmetric manner, affecting the axillae, groin, abdomen, submammary areas, and the flexor aspects of the limbs, and rarely affect the face, palms of the hands, and soles of the feet [45]. The pustules result in a superficial crust. Typical histopathologic features of pustular psoriasis, such as psoriasiform hyperplasia, parakeratosis, and spongiform pustules, are usually not present in cases of subcorneal pustular dermatosis [37]. Unlike GPP, patients with subcorneal pustular dermatosis do not experience systemic symptoms [46].

7 Variants of Pustular Psoriasis

Several variants of pustular psoriasis have been identified. These variants share similar clinical presentations, which involve the eruption of widespread sterile pustules of various distributions and histopathologic features [47]. However, it is worth noting that in certain countries, the classification of acrodermatitis continua of Hallopeau and palmoplantar pustulosis as variants of GPP remains controversial as they may be considered distinct disease entities. Below, we describe the key features of these variants.

7.1 Annular Pustular Psoriasis

Annular pustular psoriasis is a rare form of pustular psoriasis with a chronic relapsing disease course and usually a good prognosis [48]. The clinical presentation of annular pustular psoriasis is characterized by the appearance of erythematous lesions, usually polycyclic, with small sterile pustules on the circumference of the lesions and fine peeling. Affected areas include the trunk, proximal extremities, buttocks, and abdomen [48]. Unlike GPP lesions, annular pustular psoriasis lesions are not confluent, and patients usually present in a better clinical condition. Patients may have general systemic symptoms, such as fever, malaise, and arthralgia, but these are generally much milder than in patients with GPP [48]. Annular pustular psoriasis is usually recurrent; it has a short duration with a cyclical course, and it can recur after several years [48].

7.2 Pustular Psoriasis of Pregnancy

Pustular psoriasis of pregnancy, also known as impetigo herpetiformis, is a well-defined form of dermatosis of pregnancy that can be life threatening if not diagnosed accurately and treated promptly [24]. The classification of pustular psoriasis of pregnancy as a variant of GPP or as a distinct disease entity remains controversial [24]. Pustular psoriasis of pregnancy tends to occur early during the third trimester and mostly resolves after parturition; however, the possibility of recurrence during subsequent pregnancies is high. Patients usually present with pustules studded on erythematous patches within intertriginous areas, such as the axillae and skin folds of the breasts. Patients may experience fatigue, fever, diarrhea, delirium, elevated markers of inflammation, such as an increased erythrocyte sedimentation rate, and increased white blood cell counts. In severe cases, the rash of pustular psoriasis of pregnancy can progress to erythroderma, which can lead to dangerous fluid and electrolyte imbalances, loss of thermoregulation in the skin, and an increased risk of secondary infections and sepsis [24].

7.3 Infantile/Juvenile Pustular Psoriasis

Unlike psoriasis, which is common among infants, children, and adolescents, with a reported prevalence range of 0–2.1% [49], the incidence of pustular psoriasis in patients aged younger than 18 years is very low [47], with disease onset from early life through adolescence [50]. Similar to adults, in children and adolescents, plaque psoriasis is the most frequent psoriasis subtype (9–91.9%) compared with pustular psoriasis (0–13.1%) [49]. Infantile/juvenile pustular psoriasis may present as diffuse generalized pustules similar to adult GPP [47]; however, more commonly, it can present in a circinate or annular pattern. Children with pustular psoriasis usually present with systemic symptoms, including fever and laboratory abnormalities such as leukocytosis and an elevated erythrocyte sedimentation rate [18, 47].

7.4 Acrodermatitis Continua of Hallopeau

Acrodermatitis continua of Hallopeau is a chronic localized form of pustular psoriasis that involves the digits of the fingers and toes, most commonly the fingertips and nails, and may eventually progress to severe complications such as anonychia and osteitis [47, 51]. Acrodermatitis continua of Hallopeau, similar to GPP, is linked to specific triggers, including localized trauma to the distal portion of a digit and localized infections [47]. Although rare, acrodermatitis continua of Hallopeau can evolve into GPP when patients develop pustular eruptions across the body.

7.5 Palmoplantar Pustulosis

Palmoplantar pustulosis, a recurrent chronic inflammatory skin condition, is considered the most common form of pustular psoriasis and is characterized by erythema, scales, and pustules that affect the palms of the hands and soles of the feet, causing hyperkeratosis and skin fissuring [52]. The disease usually affects the medial and lateral borders and may also involve the fingers and toes [53]. Palmoplantar pustulosis is more prevalent in Japan compared with Western countries and is more common among female individuals and cigarette smokers [54]. The disease course is typically chronic, and at advanced stages, palmoplantar pustulosis is characterized by the presence of numerous pustules on an erythematous squamous base. The frequency of *IL36RN* variants is lower in patients with palmoplantar pustulosis (< 5%) than those with GPP [29].

8 Conclusions

The accurate diagnosis of GPP remains challenging because of its rarity, the heterogeneity of its cutaneous and systemic symptoms, and the number of differential diagnoses and variants of psoriasis from which it must be distinguished. As such, there is a clear need for standardized international guidelines to aid healthcare professionals in diagnosing GPP. Beyond the development of guidelines, advances in the discovery of GPP-specific biomarkers will allow the creation of objective quantitative strategies to define disease severity and optimize treatment regimens. For example, the recent discovery of elevated levels of high-mobility group box 1 in the serum and skin of patients with GPP may serve as a marker for disease severity upon further validation [55]. Better understanding of the biological mechanisms that lead to the development and exacerbation of GPP in patients without GPP-associated genetic mutations will allow the identification of more effective differential diagnostic strategies. In addition, for patients with GPP caused by genetic mutations, advances in our understanding of the genetics of GPP and other pustular diseases will pave the way for improved, rapid, and accurate diagnostic methods. The routine clinical implementation of genetic testing in the future will enhance our ability to define patient populations with specific GPP subtypes. Combining genetic testing with knowledge of the patient's medical history, physical examinations, laboratory tests, and histopathologic assessments will offer a powerful diagnostic method for GPP and provide pathways to diagnose and treat patients with GPP rapidly and accurately.

Declarations

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