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REVIEW

Pustular psoriasis with a focus on generalized pustular psoriasis: classification and diagnostic criteria. An Italian expert consensus

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ABSTRACT

Generalized pustular psoriasis (GPP) is a severe and life-threatening systemic disease associated with significant morbidity and mortality. Recent progress has been made in understanding the pathogenetic pathways involved in GPP and an intricate interaction between innate and adaptive immune mechanisms has been suggested. Despite formal consensus guidelines on pustular psoriasis currently available in the literature, the definitions and classifications of GPP used across studies were inconsistent. Consequently, there are no unified criteria that can be universally adopted for precise diagnosis, classification and effective treatment of GPP patients with new targeted drugs. The aim of this review was to collect all the main evidence on available diagnostic criteria for GPP and to establish recommendations in order to promote a better stratification and therapeutic management of this severe and heterogeneous disease.

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KEY WORDS: Psoriasis; Diagnosis; Consensus.

Generalized pustular psoriasis (GPP) is a severe, potentially life-threatening systemic disease characterized by sterile, neutrophil-filled pustules on erythematous base spread out on large areas of the body.[1] GPP is associated with significant morbidity and in some cases, mortality, especially in the absence of appropriate and timely treatment.

GPP is considered a rare form of psoriasis with an estimated prevalence of 7.46 patients per million in Japan[2] and 1.76 patients per million in France,[3] and represents less than 1% of all psoriasis cases.[4-7] According to both European and Asian cohort studies, GPP is approximately twice as common in women than in men and the mean age of onset of disease is 31 years.[8, 9]

Rigorous studies characterizing GPP have been limited by both the rarity of this condition and by multiple definitions and diagnostic criteria that have been suggested over the years. An additional limitation is that many cases do not have an initial dermatological approach.

GPP is traditionally classified as a clinical type of psoriasis, even though clinical, histological and genetic evidence suggests that it is a separate disease. In recent years, variations of interleukin 36 receptor antagonist (IL36RN), caspase recruitment domain-containing protein 14 (CARD14), adaptor related protein complex 1 subunit sigma 3 (AP1S3) and myeloperoxidase (MPO) genes have been identified as causative or contributing genetic defects in a significant proportion of patients affected by GPP.[10] These disease-related genes play a role in fundamental inflammatory pathways, particularly in neutrophil driven diseases. Indeed, GPP has been included among the neutrophilic dermatoses (ND), which encompass a wide spectrum of conditions characterized by the accumulation of activated neutrophils in the skin and rarely internal organs. According to a clinicopathological classification of ND, GPP represents the paradigm of epidermal ND with pustular presentation.[11]

Significant progress has been made in understanding the critical pathways involved in GPP pathogenesis and it has been defined that innate and autoinflammatory responses dominate in GPP.[12] More recently, an intricate interaction between innate and adaptive immune mechanisms in the autoinflammatory pathogenesis of GPP has been suggested.[10]

In addition, viral and pharmacological triggers can induce a shift from plaque psoriasis towards GPP.[13] GPP is characterized by numerous clinical manifestations. GPP can be associated with many systemic symptoms and extracutaneous manifestations and its severity is strictly linked to the relevance of the many associated manifestations. In the era of precision medicine in dermatology, GPP is exemplary for both challenges and chances: while new pharmacological therapies offer great hope, there is urgent need for better stratification of this severe and heterogeneous disease. Indeed, even though formal consensus guidelines on pustular psoriasis have been published by international groups, there is a need for unified criteria that can be universally adopted and allow for correct diagnosis, classification and above all for a precise and effective treatment of GPP.

To this end, a panel of Italian dermatologists with extensive experience with psoriasis and GPP convened to review available literature evidence and to establish the criteria for a correct diagnosis of GPP. This article summarizes the findings and recommendations issued from the collective work of the expert panel.

Overview of the current knowledge on GPP

GPP pathogenesis

The precise pathophysiological mechanisms behind GPP remain elusive, although increased attention in both genetic basis and immunological features have provided several insights into the underlying pathogenetic pathways and their mutual interaction. The first GPP patient was described in 1910 by Leopold von Zumbusch[14] but it was not until over 100 years later that a more precise understanding of its pathogenetic processes was reached.

The high severity of inflammation observed in patients with GPP and the description of many familial cases led to the hypothesis of a monogenic inheritance pattern.[15] In 2011, the identification of loss-of-function mutations in IL36RN gene emphasized the key role of this pathway in the pathogenesis of GPP. The acronym DITRA (deficiency of interleukin thirty-six-receptor antagonist) is often used for those cases of GPP in which IL36RN mutation is detected.[16] Pathogenic IL36RN mutations were originally identified in consanguineous GPP pedigrees of Tunisian origin and in five isolated cases from the UK.[16, 17]

Since the original description many other cases have been described from Europe, North America and Japan.[2, 3, 18, 19]

Several types of IL36RN mutations, including substitution, frameshift, and splicing defects, have been reported as the causative genetic background in some GPP cases in different geographical regions.[16, 17, 20-22]

The IL-1/IL-36-chemokine-neutrophil axis is considered a core pathogenic molecular pathway in GPP[23] and involves activation of IL-1 and IL-36 signaling while in plaque psoriasis it is the IL-17/IL-23 axis that plays a central pathogenetic role.[24]

The different subtypes of psoriasis are thought to exist within a continuum. In plaque psoriasis adaptive immunity has a key role with the IL-17/IL-23 pathway at the forefront.[24] Conversely, in GPP, it is the innate immune responses involving IL-36 activation, neutrophil infiltration, and autoinflammation that is central to the pathogenesis.[25]

The pathogenesis of GPP partly overlaps with the typical pathways of psoriasis vulgaris but exhibits a more pronounced activation of the innate immune system: cytokines such as IL-17A, IL-22, IL-23, and anti-tumor necrosis factor (TNF)-α were found to be elevated in both

plaque psoriasis and GPP; however, GPP lesions have significantly higher IL-1 and IL-36, and lower IL-17A and IFN-γ messenger RNA expression levels than plaque psoriasis lesions.[23]

Further research on the interplay between IL-17- and IL-36-driven inflammation has shed a new light on how individual mediators may modify the spectrum of psoriasis via shifting innate to adaptive immunity or *vice versa*.[26] Arakawa *et al.* suggested a link between the innate and adaptive immune system in the pathogenesis of GPP by demonstrating an enhanced proliferation of IL-17 producing CD4+ T-cells via IL-36 signaling.[27]

IL36RN mutations do not appear to correlate to the risk of developing plaque psoriasis. In fact, most IL36RN mutations are identified in patients with GPP that do not suffer from concurrent plaque psoriasis.[28]

Clinical course of GPP

GPP is characterized by recurrent eruptions of widespread sterile, macroscopic pustules that occur either with or without systemic inflammation and symptoms. Age at onset, precipitating factors, natural history and severity vary widely among GPP patients.

Several consensus guidelines on GPP have been published by European and Japanese groups in order to distinguish GPP from other variants of pustular psoriasis[1, 29] as well as other diseases or reactions associated with pustular eruptions.

In 2017, the European Rare and Severe Psoriasis Expert Network (ERASPEN) published the first European consensus statement on the phenotypes of pustular psoriasis (Table I).[1]

GPP was defined by the presence of primary, sterile, macroscopically visible pustules on non-acral skin, corresponding to neutrophil collections on histology. In addition to this, the criteria included subclassifiers concerning the presence/absence of systemic inflammation and psoriasis vulgaris, and specified that a diagnosis of GPP can only be made when the condition has relapsed (>1 episode) or persisted (for more than three months).[1] According to Japanese guidelines GPP is diagnosed based on the following parameters (definitive diagnosis if all four parameters are present; suspected diagnosis with two or three parameters):[29] 1) systemic symptoms such as fever and fatigue; 2) systemic or extensive flushing accompanied by multiple sterile pustules that sometimes merge to form lakes of pus; 3) neutrophilic subcorneal pustules histopathologically corresponding to Kogoj's spongiform pustules; and 4) repeated recurrence of the above-stated clinical and histological findings.[30] Table II summarizes the similarities and differences between the Eraspen and Japanese diagnostic criteria for GPP.[1, 29]

TABLE I.—*Consensus definitions for the diagnosis of pustular psoriasis.*

Generalized pustular psoriasis	
Primary, sterile, macroscopically visible pustules on non-acral skin (excluding cases where pustulation is restricted to psoriatic plaques)	
Subclassifier	With or without systemic inflammation
Subclassifier	With or without psoriasis vulgaris
Subclassifier	Either relapsing (>1 episode) or persistent (>3 months)
Palmoplantar pustulosis	
Primary, persistent (>3 months), sterile, macroscopically visible pustules on palms and/or soles	
Subclassifier	With or without psoriasis vulgaris
Acrodermatitis continua of Hallopeau	
Primary, persistent (>3 months), sterile, macroscopically visible pustules affecting the nail apparatus	
Subclassifier	With or without psoriasis vulgaris

Adapted from Navarini *et al.*[1]

In 2016, a German group published a very comprehensive review on the relevance of a correct differential diagnosis between GPP and other types of pustular psoriasis (Table III).[31] The authors argued that some types of pustular psoriasis, including GPP, share clinical, pathogenetic and epidemiological aspects with plaque psoriasis.

GPP often presents in individuals with a pre-existing history of plaque psoriasis.[32] Rarely, typical plaque psoriasis appears after GPP has arisen.[15]

Plaque psoriasis may develop into GPP after many years. The role of multiple trigger factors, including pregnancy, infections, drugs and electrolyte imbalances, has been described in case reports and case series. Concerning infectious triggers, upper respiratory tract infections, viral infections caused by varicella zoster virus and Epstein-Barr virus as well as superficial cutaneous mycoses have been linked with the development of GPP.[33-35]

TABLE II.—*Summary of diagnostic criteria.*[1, 29]

	Systemic symptoms	Skin symptoms (Pustules)	Histology	Laboratory abnormalities	Recurrence	Plaque psoriasis
JDA 2018[29]	+	+	+	-	+	-
ERASPEN[1]	±	+	-	-	+	±

TABLE III.—*Pustular psoriasis.*

Pustular psoriasis	
	Other designations/names
Generalized forms	
Generalized pustular psoriasis (GPP)	Von Zumbusch type
Special forms of GPP	
• Impetigo herpetiformis	GPP occurring in pregnancy
• Annular pustular psoriasis	Erythema annulare centrifugum-type psoriasis with pustules
• Paradoxical GPP following biologic therapy	
Localized forms	
Acrodermatitis continua of Hallopeau (ACH)	Hallopeau's disease
Acute generalized pustular bacterid	Andrews bacterid
Palmoplantar pustulosis (PPP)	Palmoplantar psoriasis of Barber-Königsbeck
Paradoxical PPP following biologic therapy	

Adapted from Weisenseel *et al.*[31]

GPP has also been described following Sars-Cov-2 infection.[36]

Regarding pharmacological triggers, both administration and discontinuation of certain drugs can precipitate GPP flares, the best example being withdrawal of systemic glucocorticosteroids in patients with plaque psoriasis.[37, 38] Likewise, withdrawal of cyclosporine has also been reported to lead to GPP flares.[39, 40] Several other medications have been associated with GPP, including antibiotics (amoxicillin, penicillin),[41, 42] antihypertensives (propranolol, ramipril),[43, 44] and biologic agents such as anti-TNF-α monoclonal antibodies and ustekinumab.[45-48] Indeed, anti-TNF-α-induced psoriasis represents the most frequent form of paradoxical skin reaction, *i.e.*, the development of inflammatory immune-mediated skin manifestations in patients treated with biologics for rheumatological and gastroenterological indications.[49, 50]

Several case reports also suggest the contribution of electrolyte disorders, particularly hypocalcemia due to hypoparathyroidism, in triggering GPP.[51-53]

The clinical course of GPP is highly variable and in general without treatment is unstable and long lasting. Even if there are disease free periods, over the years, those are often interrupted by recurrences of pustular flares. Among patients with GPP across two tertiary hospitals 76% experienced a relapse of skin lesions after initial clearance (following treatment) over a 1-year follow-up period.[9]

In 1971, TJ Ryan reported a 25% mortality rate for GPP, attributable both to the disease itself and its treatment.[54] In recent reports this rate dropped to 2%-16%.[3, 29, 51, 55] As the knowledge on GPP pathogenesis expands, the development of targeted therapies such as biologics holds promise for its successful treatment in the near future.

Methodology

An Italian panel of ten experts in the fields of Dermatology with extensive experience in psoriatic diseases was assembled for two online meetings in May 2021. As there is no consensus over the precise diagnostic criteria that define GPP, the goal of the Italian experts was to provide all specialists who deal with the management of patients with GPP with a reliable guidance for a correct diagnosis of the disease by integrating the best available evidence.

A focus group activity was used which consisted of three main phases: 1. Preliminary analysis of the literature, which allowed the selection of the most relevant articles on the diagnosis of GPP; 2. Identification of the main aspects/topics relating to the GPP diagnosis; 3. Elaboration of the expert recommendations on a number of adequate criteria for the diagnosis of GPP.

Expert opinion

Classification of pustular psoriasis

The German classification clearly differentiates generalized from localized pustular psoriasis and includes, for both, a subtype that is observed upon treatment with biological agents (paradoxical pustular psoriasis).[31] The infantile and juvenile subtype of GPP should also be considered and added to the framework provided by the German group. Furthermore, the paradoxical subtype needs to be redefined for both generalized and localized pustular psoriasis, as it can be triggered by pharmacological therapy in general rather than just biologic agents.

Essential aspects of an accurate GPP diagnosis

The diagnosis of GPP should be suspected in patients with acute onset erythema and pustulosis, and subsequently confirmed through clinicopathologic correlation. Physical examination, which is important to assess the extent of skin involvement, should always be complemented by an accurate review of clinical symptoms and patient history, as well as histopathological and laboratory data (Figure 1).

Clinical signs and symptoms

Clinical signs and symptoms differ between pure forms of GPP and those associated with chronic plaque psoria-

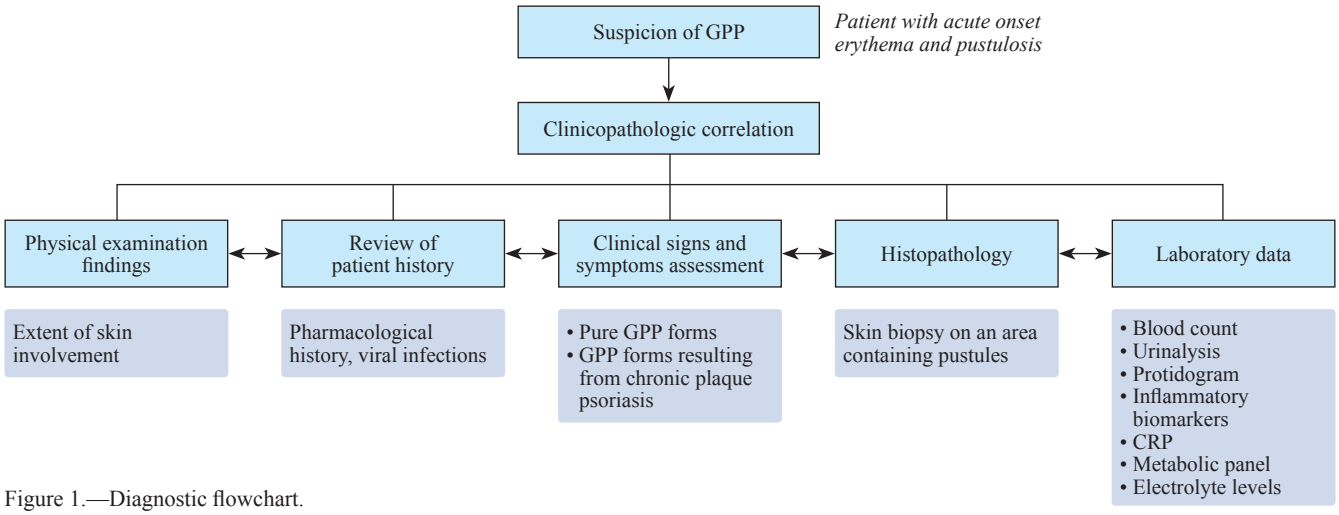

Figure 1.—Diagnostic flowchart.

sis. Pure GPP forms are much rarer than those developing in the setting of chronic plaque psoriasis and present systemic symptoms such as fever, joint pain, risk of sepsis, general distress, fatigue and in some cases an electrolyte imbalance.

In individuals with a history of plaque psoriasis, the development of GPP represents the coexistence of two different diseases, in which GPP becomes a medical emergency. In these patients some degree of leukocytosis, elevated Erythrocyte Sedimentation Rate (ESR) and C-reactive protein (CRP) levels may be seen, but severe systemic symptoms are usually absent.

The diagnosis of GPP can be made at the first occurrence of the disease: a flare usually begins with sudden onset, widespread erythema studded with 2-3 mm sterile pustules. An accompanying burning sensation is usually reported. History of previous episodes/flares should be investigated in order to correctly subclassify patients based on the course of the disease (*i.e.*, relapsing, persistent).

Histopathology

A skin biopsy performed on an area with pustular lesions is important to confirm the diagnosis. Histopathology reveals epidermal psoriasisform hyperplasia, with parakeratosis, acanthosis, elongation of rete ridges, diminished stratum granulosum, and thinning of the suprapapillary epidermis. In addition, a superficial dermal infiltrate of mononuclear cells, with numerous neutrophils migrating from papillary capillaries to the epidermis, leading to the formation of subcorneal pustules (spongiform pustules of Kogoj), is characteristic. In general, dermal edema and inflammatory cell infiltrates are notably greater than what is observed in plaque psoriasis.[56, 57]

Laboratory data

Laboratory evaluations are strongly suggested and deemed necessary to assess for severity and potential complications associated with GPP.

Both erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP) are elevated in GPP, and leukocytosis with neutrophilia is very common.[51]

Therefore, common initial assessments must always include complete blood count, CRP as well as urinalysis and protidogram.

Blood cultures should also be performed for clinical cases with high fever and distress.

A comprehensive metabolic panel is also required to evaluate for hypocalcemia, other electrolyte abnormalities, hypoalbuminemia, and to evaluate renal and liver function. Indeed, GPP patients may have increased alkaline phosphatase, transaminases, and bilirubin levels.[58, 59] It should be noted that hypocalcemia can occur also as a result of hypoalbuminemia, but ionized calcium is typically normal and patients are asymptomatic in this case.[32, 59]

Differential diagnoses

For the accurate clinical diagnosis of GPP, several cutaneous pustular diseases should be excluded (Table IV, Figure 2, 3, 4).

TABLE IV.—*Differential diagnoses for pustular psoriasis types.*

Types of pustular psoriasis	Differential diagnoses
GPP	1. Drug reaction (primarily AGEP) 2. Infectious diseases (bacterial viral or fungal) 3. Autoimmune bullous diseases (pemphigus foliaceus, IgA pemphigus, *dermatitis herpetiformis Duhring*) 3. Sneddon-Wilkinson subcorneal pustulosis 4. Inflammatory diseases with pustulation (pustular miliaria, eosinophilic pustular folliculitis – Ofuji disease) 5. other forms of psoriasis with pustulation and other forms of pustular psoriasis 6. *Synovitis, acne, pustulosis, hyperostosis,* and *osteitis* (SAPHO) 7. Amicrobial pustulosis of the folds (APS) 8. Langerhans cell histiocytosis (LCH)
Acrodermatitis continua of Hallopeau	1. Paronychia 2. Herpetic whitlow 3. Bacterial and fungal infections
Palmo-plantar pustulosis	1. Dyshidrotic eczema, allergic contact dermatitis/ *irritant contact dermatitis* 2. Infectious diseases (dyshidrotic eczema, tinea manuum and pedis) 3. *Keratoderma blennorrhagicum*

Conclusions

GPP includes a spectrum of conditions ranging from the classical form characterized by a clinical picture of relapsing generalized pustular lesions with or without signs of systemic inflammation, to the forms with associated plaque psoriasis with more or less widespread pustular skin involvement. Between these two extremes a number of intermediate clinical pictures can be seen. Studies are currently underway to evaluate the possibility of treating more and more GPP patients with new targeted drugs.

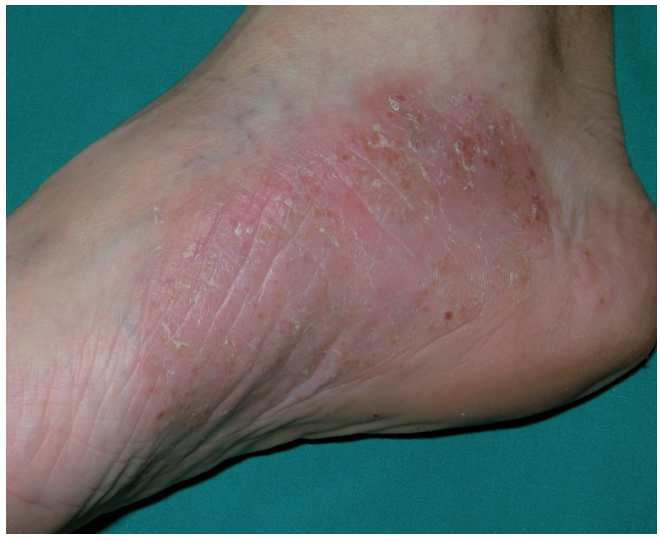

Figure 3.—Palmoplantar pustulosis.

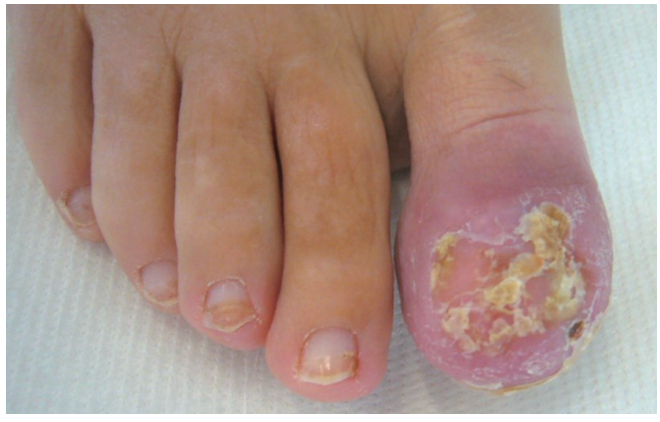

Figure 4.—*Acrodermtitis continua Hallopeau*.

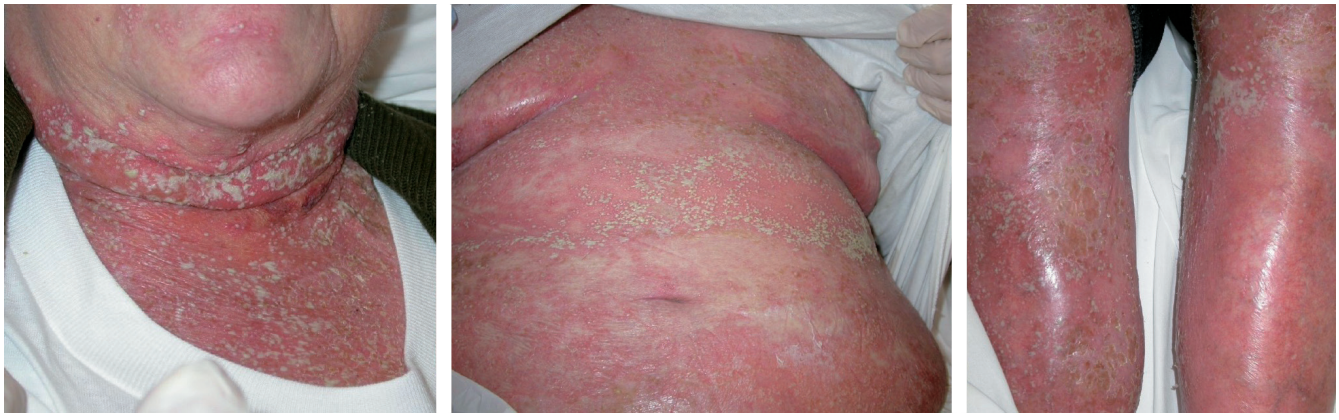

Figure 2.— Generalized pustular psoriasis.

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