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REVIEW

Diagnosis and screening of patients with generalized pustular psoriasis

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Abstract: Generalized pustular psoriasis (GPP) is a rare and potentially life-threatening variant of psoriasis that is characterized by recurrent, acute onset, widely distributed pustular eruptions on inflamed, erythematous skin. It is important to recognize acute GPP as a subtype of psoriasis associated with high morbidity and mortality so therapy can be initiated without delay. Since GPP was first described in 1910 by Leopold von Zumbusch, it has been inconsistently defined, stratified, and diagnosed in the literature. Multiple definitions and diagnostic criteria have been proposed over the years. Recently, formal consensus guidelines on GPP have been published by international groups. This article reviews the current evidence and understanding in the diagnosis and screening of GPP.

Keywords: generalized pustular psoriasis, acute generalized pustular psoriasis of von Zumbusch, pustular psoriasis, diagnostic criteria

Introduction

Generalized pustular psoriasis (GPP) is a rare, severe, and potentially life-threatening variant of psoriasis that is characterized by recurrent, acute onset, widely distributed pustular eruptions on inflamed, erythematous skin. Prompt diagnosis of GPP may prevent morbidity from complications including sepsis, acute renal failure, high-output congestive heart failure, and acute respiratory distress syndrome.[3] This article reviews the current evidence and understanding in the diagnosis and screening of GPP.

Background

In contrast to chronic plaque psoriasis, which accounts for the majority of psoriasis vulgaris (PV) cases worldwide, GPP is considered to be a rare disease. A 2018 Japanese epidemiological analysis reported that GPP represented just 1.8% of all clinical types of psoriasis.[4] However, the exact prevalence of GPP is unknown. One reason for this is that since its first description in 1910 by Leopold von Zumbusch,[1] it has been inconsistently defined, stratified, and diagnosed in the literature.[2] Rigorous studies characterizing GPP have been limited by both the rarity of the disease and by multiple definitions and diagnostic criteria that have been proposed over the years.

Historically, pustular psoriasis has been classified as either generalized or localized. The generalized forms are then further stratified by the acuity of presentation, acute GPP (also known as GPP, generalized pustular psoriasis of von Zumbusch, or von Zumbusch type GPP) and subacute GPP (also known as annular pustular psoriasis (APP) or annular pattern GPP).[5–7]

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Acute onset GPP is the most common type, which accounts for more than two-thirds of GPP cases.[3,8] When acute GPP occurs in pregnancy, it is often termed impetigo herpetiformis (IH). Juvenile pustular psoriasis (JPP) is a subtype of GPP that occurs in the pediatric population.[9,10]

Although some studies have included APP as a variant of GPP, this is controversial due to its subacute course and mild systemic symptoms.[11] Subacute GPP is characterized by annular lesions with pustules, erythema, and scaling at the advancing edge.[3,11,12] Patients typically lack systemic symptoms and laboratory abnormalities.

GPP is also distinguished from the transient, primary pustule formation that may occur at the periphery of psoriasis plaques in PV. This may occur in patients with PV during periods of disease exacerbation or following the application of irritants, such as tars. Although this phenomenon has been termed "localized GPP" and "psoriasis cum pustulatione"[2] (psoriasis with pustules), it is generally recognized that it is not a type of pustular psoriasis.

Clinical diagnosis

The diagnosis of GPP should be suspected in patients with acute onset erythema and pustulosis, and subsequently evaluated using clinicopathologic correlation between physical examination findings, patient history, review of symptoms, and histopathology.

GPP presents as the rapid onset of widespread, erythematous, inflamed skin studded with 2- to 3-mm sterile pustules.[12] Pustules may expand and coalesce into irregular "lakes of pus." During episodes of pustulation, patients may develop abnormal clinical findings associated with systemic inflammation. Patients appear systemically ill, with high-grade fever, chills, malaise, and anorexia.[8,11,12] Erythroderma may occur. After 1–2 days, the pustules typically resolve with residual erythema and desquamation.[3]

A physical examination of the skin and oral mucosa is important to evaluate the extent of skin involvement. Associated cutaneous symptoms may include pain, burning, and pruritus.[8] Associated mucosal findings include a geographic or fissured tongue, cheilitis, and ocular involvement (eg, conjunctivitis, uveitis, iritis).[3,13] Additional extracutaneous findings may include nail abnormalities, arthralgias, jaundice, and lower extremity edema.[15,16]

A history of concurrent or previous PV may be helpful in confirming the diagnosis; however, not all patients have a history of psoriasis. GPP may occur with or without a history of PV.[3,17,18] GPP may affect patients at any age, but most commonly affects patients in the fourth decade.[3,13,16] GPP is also reported to occur at a higher incidence in women.[16,18]

Although many cases appear to be idiopathic, medications, infections, and pregnancy have been reported as triggers of GPP.[3,8,12] A detailed drug history is important as it can associate the initiation or withdrawal of a drug with the onset of disease.[3,7] Rapid tapering of systemic corticosteroids is a well-known and frequently reported trigger for GPP flares.[19,20] Many other medications have also been implicated as a trigger, including antibiotics such as amoxicillin,[21] terbinafine,[22] calcipotriol ointment,[23] betamethasone ointment,[23] tumor necrosis factor-alpha (TNF-α) inhibitors,[24,25] ustekinumab,[24,26] and withdrawal of cyclosporine.[27]

Infections reported as potential etiological factors in GPP include streptococcal,[28] Trichophyton rubrum,[29] cytomegalovirus,[30,31] Epstein-Barr virus,[32] and varicella-zoster virus.[33] GPP has also been associated with various medical conditions including Turner syndrome,[4] hypoparathyroidism,[34] hypocalcemia,[34] allogeneic stem cell transplantation,[35] rheumatoid arthritis,[36] and cardiomyopathy.[4]

On initial evaluation, it is important to determine which patients require immediate hospitalization due to risk of complication. Systemic symptoms including fever, chills, shortness of breath, and altered mental status may indicate the need for inpatient admission. Obtaining a history of comorbid medical conditions may also help triage patients who are at higher risk for complications. These include advanced age, congestive heart failure, renal insufficiency, diabetes mellitus, or immunodeficiency.

Patients with GPP may develop life-threatening complications, including sepsis, acute renal failure, neutrophilic cholangitis, high-output congestive heart failure, acute respiratory distress syndrome, and death.[3,8] Mortality in GPP is most commonly due to complications from sepsis, acute respiratory distress syndrome, and cardiac failure.[3,17] It is therefore critical to identify which patients require hospitalization for stabilization, rapid treatment, and to reduce morbidity and mortality.

There is no cure for GPP. GPP may be relapsing, with recurrence either idiopathic or only when exposed to a trigger, or persistent, with symptoms lasting for months. Symptoms may self-resolve or require aggressive treatment.[8]

Laboratory abnormalities

Laboratory evaluations are strongly recommended and deemed necessary to assess for severity and potential

complications associated with GPP. Laboratory abnormalities would be consistent with the systemic involvement seen in GPP, the most common of which are leukocytosis with neutrophilia and elevated erythrocyte sedimentation rate (ESR).[3] Complete blood count with differential (to evaluate for leukocytosis and lymphopenia) and a comprehensive metabolic panel (to evaluate for hypocalcemia, other electrolyte abnormalities, hypoalbuminemia, and to evaluate liver and renal function) are common initial assessments. Skin desquamation and epidermal barrier disruption may result in electrolyte abnormalities. Hypocalcemia can occur as a result of hypoalbuminemia, but ionized calcium is typically normal and patients are asymptomatic.[8,12] Patients may have increased alkaline phosphatase, transaminase, and bilirubin levels.[6,8] Patient who report an antecedent upper respiratory infection may have positive anti-streptolysin titers.

Cultures of pustules and blood samples, gram stains, and potassium hydroxide preparation can also be performed to rule out other causes of pustulosis.[17]

Histopathology

Skin biopsy is important to confirm the diagnosis of GPP.[38] The histopathology of GPP is characterized by Kogoj's spongiform pustules, which are the accumulations of neutrophils under the stratum corneum, as well as the classic findings of psoriasis, which include parakeratosis, acanthosis, hyperkeratosis, elongation of rete ridges, diminished stratum granulosum, capillary dilation of the papillary dermis, Munro's microabscesses, and superficial perivascular mononuclear cell infiltrations. The edema and inflammatory cell infiltrate is notably greater than what is observed in PV.[11,37–39]

Other diseases with similar histopathology include acute generalized exanthematous pustulosis (AGEP). However, the additional presence of eosinophils and necrotic keratinocytes, which are suggestive of an underlying drug trigger, would likely be seen.[40]

Differential diagnosis

The list of differential diagnoses for GPP is vast and includes many cutaneous pustular diseases, including AGEP, subacute annular pustular psoriasis (APP), localized forms of pustular psoriasis (eg, palmoplantar pustular psoriasis, Acrodermatitis continua of Hallopeau), pemphigus foliaceus, IgA pemphigus, and subcorneal pustular dermatosis.[11,38]

The most important diagnosis to exclude is AGEP, a rare and severe pustular skin reaction, most commonly due to medications.[41] It presents as sterile pustules on an erythematous base and can be clinically and histologically difficult to differentiate from GPP. Clinically, AGEP has a more abrupt onset, shorter duration, does not recur, has no personal or family history of PV, and is associated with a recently initiated medication.[38,41] AGEP may also be accompanied by blood eosinophilia.[38]

Genetic screening

Although the etiology of GPP remains to be fully elucidated, a genetic basis that may cause or contribute to pustular variants of psoriasis, distinct from that of chronic plaque psoriasis, has been identified.

In recent years, genetic studies have identified three gene mutations in one or more forms of pustular psoriasis-mutations in IL36RN (encodes IL-36 receptor antagonist), CARD14 (encodes a keratinocyte adaptor protein), and AP1S3 (encodes a subunit of the adaptor protein 1 complex). These three mutations account for fewer than 30% of GPP cases.[42] IL36RN mutations are the most frequent genetic abnormality observed in pustular psoriasis and occur in approximately 20% of GPP patients.[43] AP1S3 and CARD14 variants are found in fewer than 10% of these patients.

Currently, genetic screenings for IL36RN, CARD14, and AP1S3 mutations are not routinely indicated. However, IL36RN mutations are being increasingly used to aid in the diagnosis of GPP. Genotype–phenotype studies have shown that IL36RN mutations are associated with an earlier age of onset in GPP, widespread inflammation, and are not associated with concurrent PV.[18,43,44] When this clinical triad is present in familial IL36RN mutations, it is described by the acronym DITRA (deficiency of the interleukin 36 receptor antagonist).[45] Twelves et al demonstrated that IL36RN mutations were associated with an earlier age of onset across all pustular psoriasis subtypes, with the youngest age of onset found in GPP patients (mean age of onset 31 years ±19.7 years). Based on this finding, this study recommended that patients who present with GPP before age 30 be screened for IL36RN mutations.[18]

Proposed diagnostic criteria

Recent consensus guidelines on GPP have been published by European and Japanese groups in order to distinguish GPP from other pustular diseases (Table 1). One goal of these guidelines is to develop an extended cohort using standard classification in order to reveal clinical and genetic

Table 1 Summary of diagnostic criteria

	Year	Diagnostic Criteria
Umezawa et al[37]	2003	1. Systemic symptoms such as fever and malaise 2. Multiple, isolated septic pustules on erythematous skin 3. Kogoj's spongiform pustules are histopathologically confirmed 4. Laboratory abnormalities, including left shift leukocytosis, elevated ESR, elevated C-reactive protein (CRP), elevated anti-streptolysin O antibody levels, elevated IgG or IgA, hypoproteinemia, hypocalcemia 5. Recurrence of these clinical and histological findings
Navarini et al[2]	2017	Primary, sterile, macroscopically visible epidermal pustules on non-acral skin Subclassifiers 1. With or without systemic inflammation 2. With or without plaque psoriasis 3. Either relapsing (>1 episode) or persistent (>3 months)
Fujita et al[14]	2018	1. Systemic symptoms such as fever and fatigue 2. Systemic or extensive flush accompanied by multiple sterile pustules 3. Neutrophilic subcorneal pustules histopathologically characterized by Kogoj's spongiform pustules 4. Recurrence of these clinical and histological findings A definitive diagnosis of GPP can be made in patients with all 4 features. GPP would be suspected in those with features 2 and 3.

Abbreviations: ESR, erythrocyte sedimentation rate; GPP, generalized pustular psoriasis.

insights into patient demographics, clinical features, and genetic mutations that may improve diagnosis and early treatment of this potentially life-threatening disease.

In 2017, the European Rare and Severe Psoriasis Expert Network (ERASPEN) published the first European consensus statement[2] on the phenotypes of pustular psoriasis. GPP was defined as primary, sterile, macroscopically visible pustules on non-acral skin. In addition to this, the criteria included subclassifiers that indicate if GPP occurs with or without PV and with or without systemic inflammation. The criteria also specify that a diagnosis of GPP can only be made when the condition has relapsed or persisted for more than three months. No severity assessment was published with this report. However, ERASPEN did acknowledge the need for updated severity criteria. It was thought that using the number of pustules present to measure severity would be limited by the diverse morphology of GPP, which may include either discrete or confluent pustules. If a patient presents with mixed types of pustular psoriasis (eg, both GPP and a localized form of pustular psoriasis, such as Arodermatitis continua of Hallopeau), then the patient should be classified according to the most predominant feature.

The Japanese guideline was published in 2018 by the Japanese Dermatological Association and the Study Group for Rare Intractable Skin Diseases as an update to Umezawa et al's[37] 2003 GPP guideline. This guideline by Fujita et al defines GPP as a rare disease in which acute fever, generalized skin rashes, and many sterile pustules develop. Histopathologically, GPP forms subcorneal pustules characterized by Kogoj's spongiform pustules. GPP may or may not be preceded by PV and is characterized by repeated disease recurrence. During the course of the disease, patients have abnormal clinical findings associated with systemic inflammation and often present with mucosal symptoms and arthritis as complications. Although rare, GPP may be accompanied by certain eye symptoms and secondary amyloidosis.

Fujita et al made a few important additions to the definition of GPP. The definition was updated to include that GPP may have potential complications of arthritis, mucosal and ocular symptoms, and secondary amyloidosis. This addition to the definition was made to emphasize that GPP involves more than just skin lesions, it causes systemic inflammation and has the potential for serious complications. Another significant difference between the 2003 and 2018 Japanese criteria was the removal of laboratory abnormalities from the criteria. This was due to insufficient sensitivity and specificity of laboratory abnormalities in the diagnosis of GPP; instead, laboratory abnormalities were strongly recommended and deemed necessary to assess for severity and potential complications (Table 2).

Conclusion

The diagnosis of GPP can be challenging due to its rarity, heterogeneous presentation, and lack of consistent classification, but it is important to recognize acute GPP as a potentially fatal subtype of psoriasis so therapy can be initiated without delay. GPP is diagnosed based on the presence of visible pustules on erythematous skin with

Table 2 Summary of assessments included in criteria

	Systemic symptoms	Pustules	Histology	Laboratory abnormalities	Recurrence	PV
Umezawa et al[37]	+	+	+	+	+	–
Navarini et al[2]	±	+	–	–	+	±
Fujita et al[14]	+	+	+	–	+	–

Notes: + indicates present; ± indicates present or absent; - indicates absent.
Abbreviation: PV, psoriasis vulgaris.

confirmation from histopathology, and supportive evidence from laboratory and genetic evaluations. The most important diagnosis to exclude is AGEP.

These findings are reflected in recent consensus guidelines by the ERASPEN and the Japanese Dermatological Association.[2,14] Both guidelines share two features: the clinical presence of pustules and disease recurrence. Other requirements for diagnosis such as systemic inflammation, Kogoj's spongiform pustules, and laboratory abnormalities vary depending on the criteria used.[14,37,46] These diagnostic criteria can be utilized for the assessment and diagnosis of GPP, but there remains a need for a unified diagnostic criteria that can be universally adopted and allow for further characterization of GPP in larger cohorts. Further genetic studies are needed to determine the clinical significance of known genetic mutations in the classification, diagnosis, and screening of GPP.

Disclosure

The authors report no conflicts of interest in this work.

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