Generalized Pustular Psoriasis, Acute Generalized Exanthematous Pustulosis, and Other Pustular Reactions: A Clinical Review

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KEYWORDS

• Generalized pustular psoriasis • Acute generalized exanthematous pustulosis
• Pustular skin eruptions • IL-36 pathway • Genetic mutations • Drug-induced reactions
• Biologic therapies

KEY POINTS

- Few skin conditions are as impressive as generalized pustular psoriasis (GPP), acute generalized exanthematous pustulosis, and other pustular reactions.
- However, they also pose important diagnostic and treatment challenges. All of these diseases produce disseminated and rapidly evolving pustules, usually coupled with systemic symptoms and inflammation.
- GPP is defined by sterile, macroscopically visible, non-acral pustules. It can be associated with plaque-type psoriasis and often produces systemic inflammation.

INTRODUCTION

Few skin conditions are as distinctively memorable as generalized pustular psoriasis (GPP), acute generalized exanthematous pustulosis (AGEP), and other pustular reactions.[1,2] However, they also pose important diagnostic and treatment challenges. All of these diseases produce disseminated and rapidly evolving pustules, usually coupled with systemic symptoms and inflammation. GPP is defined by sterile, macroscopically visible, non-acral pustules. It can be associated with plaquetype psoriasis and often produces systemic inflammation.[3,4] Initially considered a subtype of psoriasis, it is now understood that GPP has unique genetic and clinical features that distinguish it from common plaque psoriasis (PV). Flares of GPP are not usually associated with specific situations, but triggers have been described, among them drugs, infections, or sudden withdrawal of systemic glucocorticoids.[5,6] The rapid clinical progression

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and severity of the disease require a timely and accurate diagnosis. The diagnosis of GPP should be made with accordance to the widely used criteria, namely the European Rare and Severe Psoriasis Expert Network (ERASPEN) criteria.[7] Due to the large clinical overlap with AGEP, a working diagnosis of "putative GPP/AGEP" should be used until a persistence of greater than 3 months or a relapse of pustules is confirmed.[7] This working diagnosis may also justify systemic treatments for GPP in cases of severe disease.

AGEP[1] belongs to the severe cutaneous adverse reactions (SCARs). It is almost always drug-induced.[8–10] Patients present with multiple sterile, nonfollicular, small pustules on erythematous skin. Upon stopping the offending drug, AGEP usually resolves spontaneously in most clinical situations. Severe cases may require systemic treatment. The rapid progression and potential for systemic involvement require early confirmation of the diagnosis and oftentimes inpatient treatment.

Other pustular drug reactions include drug reaction with systemic symptoms (DRESS), pustular forms of erythema exsudativum multiforme (EEM) and Stevens-Johnson syndrome/toxic epidermal necrolysis (SJS/TEN). The key to managing these reactions is prompt identification and discontinuation of the offending drug, as well as initiating immunosuppression medications in some cases. The prevalence of these conditions is not well-defined, partly due to their rarity and the overlap in clinical features that may lead to misdiagnosis. The morbidity associated with these pustular eruptions, the potential for systemic involvement, and the challenges posed in the differential diagnosis underscore the need for a keen understanding of their pathophysiology.

Lastly, we will discuss the clinical differential diagnosis of nondrug-induced pustular reactions such as subcorneal pustulosis, pustular Sweet syndrome, amicrobial pustulosis of the folds, as well as infectious folliculitis.

The aim of this article is to discuss these complex pustular dermatoses, specifically their etiology, pathophysiology, clinical presentation, diagnostic challenges, and therapeutic strategies. A summary of these conditions is presented in **Table 1**.

PATHOPHYSIOLOGY, TRIGGERS

The pathogenesis of GPP is closely linked to dysregulation of the immune system, in particular the interleukin (IL)-36 pathway, a member of the IL-1 cytokine family.[11] This has identified it as an autoinflammatory disease, which means it produces unprompted inflammation without an identifiable antigen. The link has been proven by the highly significant association of GPP with damaging homozygous mutations in the *IL36RN* gene.[12,13] The gene product is the IL-36 receptor antagonist. When this protein is dysfunctional, unopposed IL-36 signaling has been observed, leading to increased keratinocyte proliferation and the neutrophilic infiltration characteristic of GPP lesions. This prompted the name *deficiency of interleukin-36 receptor antagonist* (DITRA) for this condition.[13] This unrestrained cytokine activity drives not only pustular formation but also systemic inflammation, which can lead to the severe systemic symptoms seen in GPP. Recent genetic analyses have elucidated a triad of mutations in addition to *IL36RN*, namely *CARD14*,[14,15] *MPO,*[16] *AP1S3*,[17-19] SERPINA3/A1,[20] BTN3A3,[21] TGFBR2, all of which are implicated in the pathogenesis of GPP, albeit accounting for only a subset of cases. The *IL36RN* mutation is notable for its role in disrupting IL-36 signaling, a pathway essential for innate immune responses and inflammation. *CARD14* mutations have been implicated in the activation of the NF-kB pathway, which is central to the proinflammatory cascade. The *AP1S3* mutation has been linked to autophagy and endosomal trafficking pathways, which are critical for cell homeostasis and may influence the inflammatory milieu. The fact that these mutations are not universally present in all cases of GPP suggests a polygenic etiology and perhaps an interaction with environmental triggers. Damaging mutations in the *MPO* gene, which encodes the major neutrophil protein myeloperoxidase, have been directly linked to the pustular reaction. A novel deletion and 3 missense mutations in the *SERPINA3* gene were found to impede or reduce activity of alpha-1-antichymotrypsin on cathepsin G in pediatric-onset GPP in Asians.[22]

AGEP has a multifactorial etiology involving not only drugs but also infections, vaccinations, iodinated contrast, food such as shiitake mushroom, environmental factors such as spider bite, and, probably, a genetic predisposition.[1] Epidemiologically, AGEP has an incidence of 1 to 5 cases per million per year and is more common in women (60%). The age of onset is typically 50 to 60 years, but cases can occur at any age. Despite its acute presentation, AGEP usually resolves favorably within 2 weeks of cessation of the offending agent and appropriate treatment, although a mortality rate of 3% has been reported, mainly due to multiorgan failure or superinfection. Genetic predisposition to AGEP is evidenced by findings such as *IL36RN* mutations, which are found in 4% of AGEP cases.[23] The occurrence of the disease in different ethnic groups, with a noted predominance in certain groups, underlines the role of genetics in

Table 1
Comparison of etiology, clinical presentation, pathogenesis, chronicity, histopathology and treatments of various pustular rashes.

Feature	GPP	AGEP	DRESS, Anticonvulsant Hypersensitivity Syndrome	Sneddon-Wilkinson	EEM, TEN/SJS	Sweet Syndrome	Infectious Folliculitis	Amicrobial Pustulosis of the Folds	Other Pustular Rashes
Etiology	Genetic predisposition, triggers like infections and medication withdrawal	Drug-induced, often antibiotics, hydroxychloroquine, and others	Drug-induced, including anticonvulsants	Unknown, possibly immune-mediated	Drug-induced or idiopathic	Idiopathic, respiratory tract infections, hematologic disease, rheumatologic, gastrointestinal disease, or drug-induced	Bacterial, fungal, or viral infections	Often associated with autoimmune diseases; sterile pustules	Various, including genetic, autoimmune, and inflammatory causes
Clinical presentation	Rapid onset of widespread nonfollicular pustules, often systemic symptoms	Rapid onset of widespread nonfollicular pustules, often fever	Rapid onset of follicular pustules, fever, often drug-specific symptoms	Recurrent superficial nonfollicular pustules, annular or serpiginous patterns	Targetoid lesions, mucosal involvement in severe forms	Painful, erythematous, edematous plaques and nodules, occasionally vesiculopustular	Follicular-based erythematous pustules	Chronic recurrent eruptions of sterile pustules, primarily in skin folds	Varies
Pathogenesis	Genetic mutations (eg, *IL36RN, CARD14*)	Immune-mediated response to drugs	Immune-mediated response to drugs, including specific syndromes like anticonvulsant hypersensitivity	Unclear, potentially immune-related	Immune-mediated response, often to drugs	Immune-mediated, often neutrophilic infiltration	Infection-driven	Unknown, possibly immune-related	Depending on the condition
Chronicity	Often chronic and relapsing	Self-limiting upon drug withdrawal	Self-limiting upon drug withdrawal	Chronic, relapsing	Acute and self-limiting	Acute, may recur in some cases	Resolves with treatment of the infection	Chronic and recurrent	Varies
Histopathology	Sterile spongiform pustules of Kogoj, neutrophils in the stratum corneum, parakeratosis, psoriasiform epidermal hyperplasia, no significant papillary dermal edema, scarce or no eosinophils. Dilated, tortuous blood vessels in the papillary dermis.	Eosinophils usually present, papillary dermal edema, spongiosis, necrotic keratinocytes, mixed interstitial and mid-dermal perivascular infiltrate, usually no dilated blood vessels in the papillary dermis.	Dense perivascular lymphocyte infiltration in the dermis, and atypical lymphocytes, often interface dermatitis.	Subcorneal neutrophilic pustules without eosinophils, no spongiosis, acanthosis, or significant dermal signs of inflammation.	EEM: Several necrotic keratinocytes throughout the epidermis with surrounding lymphocytic exocytosis, mild to moderate edema and perivascular lymphocytic inflammation with occasional eosinophils/ lymphocytes. TEN/SJS: Extensive necrosis of keratinocytes, leading to full-thickness epidermal necrosis, mild inflammatory infiltrate.	Dense neutrophilic infiltrate without vasculitis, lack of epidermal involvement, edematous papillary dermis.	Follicular pustules and (peri-) folliculitis with a neutrophilic or lymphocytic infiltrate, detection of organisms with special staining.	Sterile epidermal pustulation, neutrophilic infiltrate in the dermis, diagnosis dependent on clinical setting and association with autoimmune conditions.	Variable

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Table 1
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Feature	GPP	AGEP	DRESS, Anticonvulsant Hypersensitivity Syndrome	Sneddon-Wilkinson	EEM, TEN/SJS	Sweet Syndrome	Infectious Folliculitis	Amicrobial Pustulosis of the Folds	Other Pustular Rashes
Treatment	Systemic agents, biologics targeting specific inflammatory pathways	Prompt withdrawal of the offending drug, supportive care	Prompt identification and discontinuation of the offending drug, immunosuppressive drugs	Topical corticosteroids, dapsone, or systemic corticosteroids	Withdrawal of the offending drug, systemic corticosteroids	Corticosteroids, dapsone	Antibacterial, antifungal, or antiviral agents, depending on the cause	Topical steroids, tacrolimus, systemic agents in severe cases	Dependent on the specific condition, may include immunosuppressants

AGEP. Various drugs have been reported to induce AGEP.[1] The most common drug triggers are antibiotics, particularly beta-lactams (18%–41% of cases), macrolides, and quinolones, together with other drugs such as hydroxychloroquine (13%), antineoplastics (12%), nonsteroidal anti-inflammatory drugs (5%), anticonvulsants (4%), and calcium channel blockers. Additional drugs include antiviral, antifungal, antiparasitic, anticoagulants, antiarrhythmics, antihypertensives, antipsychotics, diabetes therapy, hormonal therapy, opioids, and even topical agents.[1] The latency period between drug exposure and the onset of AGEP generally ranges from 1 to 13 days,[1] with a mean of 3 to 9 days, indicating the rapid onset of this hypersensitivity reaction. The pathogenesis is thought to begin with the generation of drug-specific T cells. Upon exposure to the drug, these T cells are activated and release a cascade of cytokines, in particular IL-8, which is chemotactic for neutrophils.[1] In contrast, recent work has identified a T cell-independent pattern recognition receptor-dependent triggered monocyte in AGEP.[24] The massive influx of neutrophils into the epidermis leads to the formation of the characteristic nonfollicular sterile pustules. The rapid resolution of AGEP after drug withdrawal supports the hypothesis that ongoing drug exposure is required to maintain the pathogenic process.

Apart from AGEP, there is a poorly defined group of other pustular drug reactions. This is a broad category that includes other SCARs that rarely present with pustules, namely DRESS, fixed toxic drug reaction, and SJS/TEN. In most of these cases, the detailed pathophysiology remains unknown.

CLINICAL FEATURES AND DIFFERENTIATION

Accurate diagnosis and differentiation between GPP, AGEP, and various other pustular reactions, including DRESS/anticonvulsant hypersensitivity syndrome, are both critical and challenging. These conditions, although distinct in pathophysiology and etiology, often present with overlapping clinical features, making their accurate identification and management difficult.[25,26]

Generalized Pustular Psoriasis

This condition presents with a diverse clinical picture, characterized by its distinct pustular eruptions[27] on various body parts, often accompanied by systemic symptoms. The ERASPEN criteria[7] were established to facilitate the diagnosis of GPP, acrodermatitis continua of Hallopeau, and palmoplantar pustulosis. GPP is characterized by the presence of widespread, visible, noninfectious pustules on the skin, typically outside of the acral extremities, and is not limited to existing psoriatic lesions (**Fig. 1**). This condition may present alongside systemic inflammatory symptoms, with or without concomitant PV, and can manifest as either recurring episodes or as a prolonged skin eruption lasting more than 3 months.

Since the publication of these criteria, new data have become available from several GPP cohorts. The ERASPEN criteria, but also newer consensus papers,[28] state that GPP produces innumerable nonfollicular pustules on the trunk, extremities, and head. Many cases demonstrate particularly intertriginous involvement. Clusters of pustules often coalesce to form larger areas of pus-filled "lakes of pus."[29–33] 76.0% the skin lesions are recurrent and do not clearly follow a flare pattern.[31] Annular GPP tends to have fewer fevers and relapses.[34] There is no clear gender predilection in GPP; a Turkish study and others found a female predominance,[33,35,36] a Korean cohort was evenly split between men and women,[31] and in a Portuguese study 61% were male, especially subjects with liver problems.[29] GPP typically starts in middle age, that is, 38.1 to 45.6 years.[31,33] Skin and joint pain are common, affecting 62.1% and 26.2% of GPP patients, respectively.[37] Lastly,

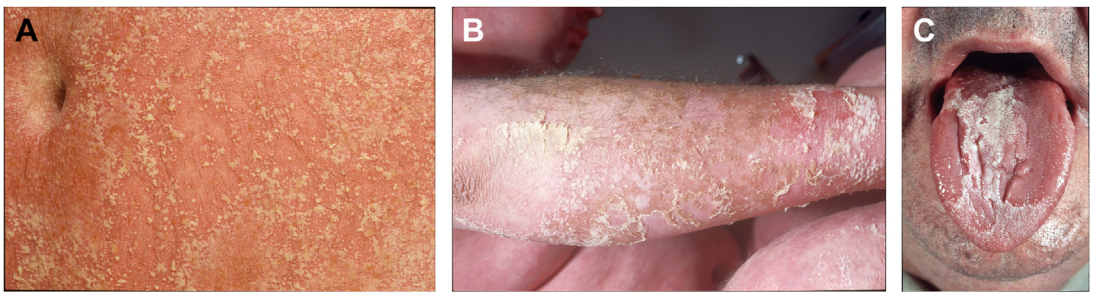

Fig. 1. Generalized pustular psoriasis (GPP) with (*A*) disseminated pustules, (*B*) lakes of pus and desquamation, and (*C*) lingua geographica that occurs in some populations, more frequently in genetically driven deficiency of interleukin-36 receptor antagonist (DITRA) with the c.115+6T > C/p.Arg10ArgfsX1 mutation.[65]

GPP can have severe consequences including miscarriages, sepsis, and death.[29,35,38]

GPP flares mostly occur without any discernible triggers. In the minority of cases, the patients report intake of certain medications such as lithium, sudden steroid withdrawal, upper respiratory infections, and pregnancy.[33,35,36] GPP is not just a skin disease but a systemic condition of intense inflammation. This is demonstrated by the elevation of C-reactive protein and leukocytosis in most patients, as well as internal manifestations that is, gastrointestinal problems.[39] Almost half of a Portuguese study group had liver enzyme abnormalities unrelated to previous medication, suggesting a direct link to GPP.[29] This study also found high white blood cell counts and a link between neutrophil levels and bilirubin, suggesting an interaction between inflammation and liver stress.[29] A recent paper stratified 416 Chinese GPP patients into 3 age groups, namely juvenile (9.5 years), middle aged (35.4 years), and seniors (62.6 years). A higher odds of a plaquetype psoriasis association was present in nonjuvenile patients. Also, juveniles had a lower incidence of comorbidities. As to the localization of lesions, juveniles had more facial, scalp, neck, and perineal lesions.[34] GPP patients without a history of psoriasis vulgaris tended to have more severe symptoms[34] and an earlier onset of disease.[36] In another Chinese study, infection and drugs were identified as presumable triggers for GPP,[36] which as confirmed in another cohort of 102 adult-onset GPP patients with systemic steroids, infections, and pregnancy as triggers.[38] In 2 studies from Malaysia, dyslipidaemia (26%), hypertension (26%), obesity (43%), and diabetes (24%) were common in pustular psoriasis (PP) patients, suggesting a link with metabolic syndrome.[32,38]

Acute Generalized Exanthematous Pustulosis

Comparatively, there are fewer data on AGEP patients. The largest study looked at 340 people, while another had 96.[40,41] Most AGEP patients are women, 56% to 68%.[40,41] The majority are white (60.6%) and non-Hispanic (70.3%), with an average age of 57.8 to 60 years.[40,41] Common symptoms include fever in 75% of patients and skin peeling in 64.7%.[40,41] AGEP produces innumerable small sterile and nonfollicular pustules that can are often focused on the intertriginous regions (**Fig. 2**). The pustules are often on edematous skin and the rash is accompanied by itch. Subsequently, desquamation follows. Medication is often the cause of AGEP, with different drugs implicated.[1,8] The latency can be as low as 24 hours, but some drugs such as hydroxychloroquine can take up to 3 weeks until the induction of AGEP. Infections were suspected triggers in a small number of cases. Liver and kidney function derangement have occurred in some cases. Treatment usually involves corticosteroids and other medications, and most patients improve. The 30-day mortality rate was 3.5%.[42] Some atypical forms of AGEP include targetoid lesion and blisters,[1] as well as a form that produces fewer but larger pustules up to 5 mm surrounded by an erythematous anulus (Navarini, personal communication). Apart from GPP and AGEP, there are also even more rare pustular reactions that must be considered. These also typically present with a rapid onset of pustules on erythematous skin.

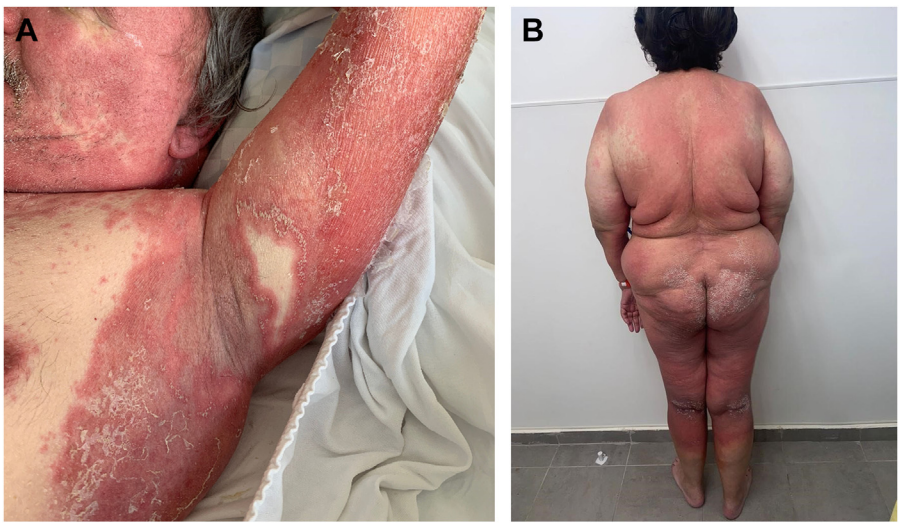

Fig. 2. Acute generalized exanthematous pustulosis (AGEP) (*A*) with disseminated pustules and (*B*) in resolution.

This similarity in initial presentation often leads to diagnostic confusion. A helpful diagnostic clue is that anticonvulsant hypersensitivity syndrome[43] (a form of DRESS) produces a follicular pustular reaction, which can help distinguish it from AGEP and GPP, as they are 2 otherwise closely related conditions. Systemic symptoms such as fever and malaise are common, further complicating the clinical picture. It is important to note that there have been cases of AGEP and DRESS overlap and AGEP and SJS/TEN overlap reported.[26,44] Diagnosis of AGEP is based on clinical and histologic criteria. A validated diagnostic scoring system for AGEP based on 3 major factors—morphology, clinical course, and histology—was published by the EuroSCAR study group.[45]

Other Pustular Conditions

Subcorneal pustulosis, or Sneddon-Wilkinson disease,[46,47] is a rare pustular dermatosis that presents with recurrent, flaccid, hypopyon-like superficial, nonfollicular pustule (**Fig. 3**), typically distributed symmetrically on the trunk, intertriginous areas, and flexures. The pustules are often arranged in annular or serpiginous patterns and can coalesce to form larger plaques. Histologically, it is characterized by subcorneal pustules filled with neutrophils without involvement of the epidermis, differentiating it from other neutrophilic dermatoses (PMID: 371657). In the ERASPEN consensus, it was grouped with GPP, and prospective data will hopefully show clearly whether it should be differentiated from GPP or not.

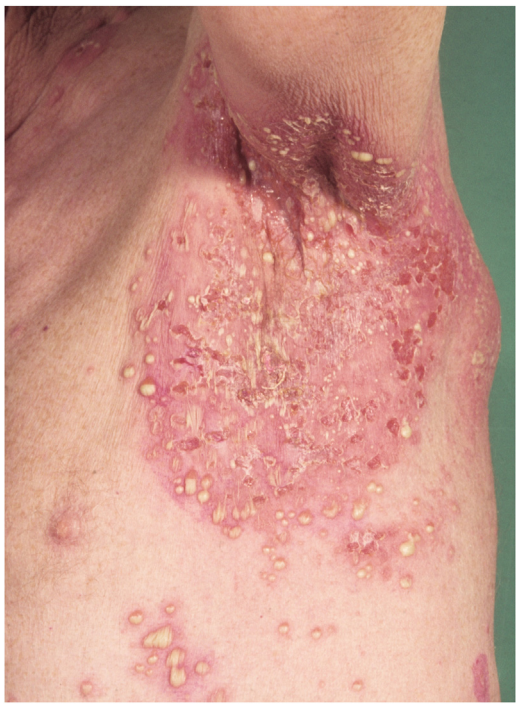

Fig. 3. Subcorneal pustulosis (Sneddon-Wilkinson). Note the "hypopyon" sign in some larger pustules.

EEM and SCARs such as SJS and TEN can also exhibit pustular lesions. There are also overlaps between AGEP and EEM.[48] These conditions are acute and often drug-induced, characterized by targetoid erythematous lesions that in severe cases progress to large-surface epidermal detachment. In TEN/SJS, the involvement of mucosal surfaces is expected.

Sweet syndrome (acute febrile neutrophilic dermatosis) is characterized by the abrupt onset of painful, erythematous, and edematous plaques and nodules, which can evolve into vesiculopustular lesions. The face, neck, and upper extremities are commonly involved. Sweet syndrome is often associated with systemic symptoms like fever and leukocytosis and can be idiopathic, drug-induced, or associated with malignancies and other systemic diseases. It can be associated with generalized pustulosis.[49,50]

Amicrobial pustulosis of the folds,[51] first described by Crickx, is another important differential that must be considered. In a study of 63 cases, a significant majority (90%) were women, with an average age of 30. In most cases, it was associated with systemic lupus erythematosus and other conditions. The condition typically presents as pustules on an erythematous (reddened) background, often eroding and predominantly affecting areas like skinfolds, the anogenital region, scalp, ears, and umbilicus. Histologically, it is characterized by a spongiform layer of subcorneal pustules and a mixed inflammatory response in the dermis.

Infectious folliculitis produce pustules arising from hair follicles and are primarily caused by bacterial, fungal, or viral agents. The lesions are typically follicular-based, erythematous, and can be pruritic or tender. Common bacterial causes include *Staphylococcus aureus* and *Pseudomonas aeruginosa*, whereas fungal folliculitis can be caused by dermatophytes or yeasts such as *Candida* species.

A detailed patient history, particularly of recent medication use, is essential in identifying potential drug-induced reactions. Skin biopsies can provide valuable information. Features such as spongiform pustules of Kogoj are indicative of GPP, whereas a dense neutrophilic and/or eosinophilic infiltrate is characteristic of AGEP. In cases of suspected drug reactions, it is important to assess the likelihood that a drug is the culprit. This involves analyzing the timing of drug administration relative to symptom onset and understanding the typical reaction profiles of the drugs involved. For GPP, genetic testing may be helpful, especially in

equivocal cases, to identify specific gene mutations associated with the disease.

DERMATOPATHOLOGY

As GPP and AGEP may not be differentiated clearly by their clinical features, a biopsy and clinicalpathologic correlations[52] are often performed. In the Japanese guideline for GPP, the presence of certain histologic features necessitating a biopsy is mandatory.[53] The histologic features of GPP include sterile spongiform pustules of Kogoj, which are defined as neutrophilic granulocytes accumulating within the stratum spinosum. Also, neutrophils are found more diffusely distributed in the stratum corneum (Munro abscesses) and in the upper dermis, and parakeratosis is expected. No significant papillary dermal edema is found. In addition, psoriasiform epidermal hyperplasia, hypogranulosis, suprapapillary plate thinning and tortuous, and dilated blood vessels in the stratum papillare may be seen especially in long-standing lesions.[52] It remains to be investigated if the later histologic changes are predominantly present in GPP patients with concomitant plaquetype psoriasis. Histology of GPP typically shows only scarce or no eosinophils. In general, in AGEP, eosinophils are typically more abundant. The first description of AGEP demonstrated 4 patients with predominantly eosinophilic pustules.[54] Other important histologic criteria that distinguish AGEP from GPP are keratinocyte necroses and a dermal edema, both of which are usually missing or only mild in GPP.[52,55] The neutrophil pustules in both GPP and AGEP are nonfollicular.[54] EEM shows necrotic keratinocytes within and above the basal layer surrounded by intraepidermal lymphocytes, a mild to moderate edema, and perivascular lymphocytes in the superficial dermis but normally no interface dermatitis. Eosinophils may be present, but they are not a diagnostic feature.[56] DRESS shows a denser perivascular lymphocytic infiltration in the dermis, as well as eosinophils and atypical lymphocytes. Often, there is an interface dermatitis present. The defining feature of TEN/SJS is extensive necrosis of keratinocytes, leading to full-thickness epidermal necrosis. The inflammatory infiltrate can be very mild, whilst interface changes defined by lymphocyte-mediated damage of the basal keratinocytes can be present. Sweet syndrome shows a dense neutrophilic infiltrate without vasculitis, a lack of epidermal involvement, whilst the papillary dermis is edematous. Subcorneal pustulosis, or Sneddon-Wilkinson disease, demonstrates subcorneal neutrophilic pustules without eosinophils. No spongiosis, acanthosis, or significant dermal signs of inflammation are expected in this condition.[57] In amicrobial pustulosis of the folds, there are sterile epidermal pustulation and a neutrophilic infiltrate in the dermis. This pattern is not distinctive and the diagnosis is dependent on the clinical setting, especially the association with autoimmune conditions. Lastly, infectious folliculitis demonstrate follicular pustules and (peri-)folliculitis with a neutrophilic or lymphocytic infiltrate, depending on the offending organisms that can be detected with special stainings.

TREATMENT

Accurately distinguishing between the various pustular conditions is important for several reasons. Specific treatments vary between these conditions. In addition, in drug-induced reactions, identification of the causative agent is essential to prevent relapses. The variety of treatments for GPP, with 17 different options identified by Noe and colleagues (2022),[37] reflects the wide range of options that were tried to control this condition. Primary options include acitretin, cyclosporine, methotrexate, and infliximab, each contributing to symptom relief and disease control. Acitretin, an oral retinoid, is a traditionally used drug for GPP[38] but is slow-acting and requires several years of contraception for women of childbearing age. Methotrexate, valued for its inflammation-reducing effects, has been beneficial in numerous GPP cases, according to retrospective studies.[38] Cyclosporine is an effective immunosuppressant but has numerous side effects when used on a long-term basis. Apremilast increases cyclic adenosine monophosphate levels intracellularly and has been shown to be useful against neutrophilic infiltrates. Monoclonal antibodies like infliximab, a TNF-alpha blocker, are effective therapies. IL-17 blockers such as secukinumab and ixekizumab are gaining attention, particularly secukinumab for its effectiveness in easing symptoms during clinical trials. Brodalumab, targeting the IL-17 receptor, has shown positive results in clinical remission and improvement. IL-23 blockers, like guselkumab, also demonstrate effectiveness, underscoring this pathway's role in GPP. Indeed, guselkumab has been registered in Japan for the treatment of GPP. However, in a retrospective study in Italy, IL-23 antagonists demonstrated inferiority to IL-17 blockers in PP.[58] The newest therapies focus on the IL-36 pathway, such as spesolimab and imsidolimab. Interestingly, they are proving effective in patients with or without *IL36RN* mutations.[59,60] After 1 week of spesoliumab, 54% of GPP patients had no more pustules, in contrast to 6% of placebo patients. A large study involving 123 patients

in 60 hospitals and clinics showed that high-dose spesolimab greatly lowers the risk and frequency of GPP flares over 48 weeks compared to a placebo. This finding underscores spesolimab's role in preventing GPP flares.[61]

For AGEP and pustular drug reactions, the main approach is to discontinue the offending drug. The first critical step is identifying and stopping the trigger medication. Alongside supportive treatments like topical steroids, control of fluid intake and fever are crucial. In more severe instances, treatments might include systemic steroids or immunosuppressants/biologics. A study by Yanes found cyclosporine as effective as systemic glucocorticoids in halting pustule formation and helping with erythema resolution, without significant side effects.[62]

INTERNATIONAL RARE AND SEVERE PSORIASIS EXPERT NETWORK PROSPECTIVE REGISTRY AND FUTURE QUESTIONS TO BE ADDRESSED

Since the rarity of GPP makes research efforts difficult, the typical clinical course and the effects of pharmacologic treatments under real-world conditions remain poorly understood. Investigational endeavors are further complicated by varying geographic prevalence.[63] Therefore, international cooperation is essential to collect sufficient samples for comprehensive analysis. Historically, the lack of clear consensus criteria and heterogeneous patient populations for GPP and other PP subtypes have impeded targeted research efforts. To address this issue, ERASPEN was established in 2012 as a cross-sectional investigation of clinical phenotypes and genotypes of PP, which resulted in a consensus[7] defining the currently established diagnostic criteria for GPP. As these criteria were not chosen based on prospective data but rather on the opinion of experts, the decision to collect such data was made. Building on this collaborative effort, the ongoing, prospective International Rare and Severe Psoriasis Expert Network (IRASPEN) registry was created in 2020. By longitudinally following patients worldwide over a period of 5 years, several unanswered questions regarding PP subtypes will be addressed, including what overlapping phenotypes exist, the actual severity and frequency of flares, as well as the effect of established treatments such as systemic steroids that are (perhaps falsely) accused of triggering GPP flares. Naturally, emerging treatments will also be evaluated with real-world evidence in this noninterventional registry. Observation of the natural course of the disease allows further phenotypic characterization by considering the evolution of clinical features. A better clinical and pathophysiological understanding can be achieved by studying the short-term and long-term responses to therapeutic interventions. In addition, biological sampling including serologic deoxyribonucleic acid , ribonucleic acid, and proteomic analyses, as well as transcriptomics of lesional and unaffected skin samples, will be used to further characterize GPP and its inflammatory pattern at the molecular level. Since the underlying mutations have mainly been analyzed in sporadic cases or large pedigrees, systematic genetic profiling of patients and their first-degree and second-degree relatives will provide new insights. Currently, 8 centers in 7 different countries on 2 continents are participating in the registry, with more to be initiated soon to join the global cooperation.[64] The authors anticipate this collaborative registry will help address current and future clinical unmet needs of GPP (apply on iraspen.org).

Taken together, the authors have delved into the complexities of diagnosing and managing GPP, AGEP, and other pustular skin reactions. These conditions, while distinctive in their pathophysiology and triggers, present significant diagnostic challenges due to overlapping clinical features. GPP is characterized by widespread sterile pustular lesions, often associated with systemic inflammation, and can be triggered by various factors including drugs, infections, or steroid withdrawal. Its pathogenesis is closely linked to immune dysregulation, notably involving the IL-36 pathway and mutations in several genes. AGEP, commonly drug-induced, presents with multiple sterile pustules and is driven by T cell and monocyte activation.[65] The key to effective management is a precise diagnosis, which hinges on patient history, skin biopsies, and understanding the nuances of each condition. Treatment strategies differ: GPP often requires systemic agents and targeted biologics, while AGEP primarily involves withdrawing the offending drug and providing supportive care. Prospective registries and clinical studies will enable greatly improved treatment strategies for these neglected conditions.

CLINICS CARE POINTS

- In patients with disseminated non-follicular pustules think about GPP and AGEP. In severe cases, a working diagnosis of GPP/AGEP can be justified for systemic treatment, until the GPP diagnosis can be confirmed.
- Patients without systemic inflammation can still have GPP or AGEP.

- Patients without plaque-type psoriasis can still have GPP.
- Withdrawal of corticosteroids might not be a frequent cause of GPP.

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DISCLOSURE

None.

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