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Best Practices

Generalized Pustular Psoriasis: An Uncommon Diagnosis Carrying an Outsize Burden of Disease

Introduction

Generalized pustular psoriasis (GPP) is a rare, severe, and potentially life-threatening systemic and chronic autoinflammatory disease characterized by sterile, neutrophilic pustules. It has been included within the spectrum of psoriasis because it is sometimes observed in conjunction with plaque psoriasis and because it involves the recruitment of T cells and neutrophils.

However, GPP is a distinct entity from its better-known counterpart, and can develop independently from, or in association with, plaque psoriasis. GPP is also distinct from plaque psoriasis in its strong association with the interleukin (IL)-36 cytokine pathway.[1] About one-third of patients with GPP present with the lesions of plaque psoriasis, suggesting a common genetic component, but the majority do not present with such lesions, suggesting a unique pathoetiology.

GPP is classified into the following types: acute (von Zumbusch variant, representing up to 90% of adult cases); pustular psoriasis of pregnancy; and infantile/juvenile pustular psoriasis. Pustular psoriasis may occur in localized forms, including palmoplantar pustular psoriasis and acrodermatitis continua of Hallopeau, the latter characterized by pustular eruptions on the tips of the fingers and toes.[2]

Epidemiology

Since its first description in 1910 by Leopold von Zumbusch,[3] GPP has been inconsistently defined, stratified, and diagnosed in the literature. Data on the prevalence and incidence in the United States are lacking and estimates are highly variable among countries in Europe and Asia. It is almost certainly underdiagnosed based on a lack of familiarity with its clinical characteristics and the reimbursement hurdles for a condition for which there is no targeted treatment.[3]

Clinical presentation and diagnosis

Although many dermatologists seldom see GPP, those who do see it are generally adept at diagnosis. A survey of dermatologists (N=29) in Europe and the United States who had seen patients with GPP revealed that most agreed about the diagnostic criteria.[4] All of them stated that pustules were necessary to diagnose a flare, with the next most cited criteria being worsening of skin lesions (83%) and erythema (76%). The most common triggering factors cited by dermatologists were steroid withdrawal (often or very often, 64%), infection (often or very often, 58%), and stress (often or very often, 50%).

GPP presents as the rapid onset of widespread, erythematous, inflamed skin studded with 2- to 3-mm sterile pustules[5] *(Figure 1)*. Pustules may expand and coalesce into irregular "lakes of pus." During episodes of pustulation, clinical findings associated with systemic inflammation may be seen. Patients appear systemically ill, with high-grade fever, chills, malaise, and anorexia. Erythroderma may occur *(Figure 2)*. After 1 to 2 days, the pustules typically resolve, with residual erythema and desquamation.[5]

Associated cutaneous symptoms may include pain, burning, and pruritus. Mucosal findings include a geographic or fissured tongue, cheilitis, and ocular involvement (eg, conjunctivitis, uveitis, iritis). Extracutaneous findings may include nail abnormalities, arthralgias, jaundice, and lower-extremity edema.

Rapid tapering of systemic corticosteroids is a well-known and frequently reported trigger for flares. Other medications that were implicated as triggers in various reports included amoxicillin, terbinafine, calcipotriol ointment, betamethasone ointment, tumor necrosis factor-α inhibitors, ustekinumab, and withdrawal of cyclosporine.

GPP and its variants may affect patients at any age, but most often occurs in patients in their 40s. It is more common in women.[3] Although rare, its possible severity and consequences should not be underestimated. GPP, especially an acute episode (flare), may be a medical emergency with potentially life-threatening complications, including hypocalcemia, acute respiratory distress syndrome, bacterial superinfection leading to sepsis, and dehydration. Given the potential severity of these complications, early and accurate diagnosis is essential.

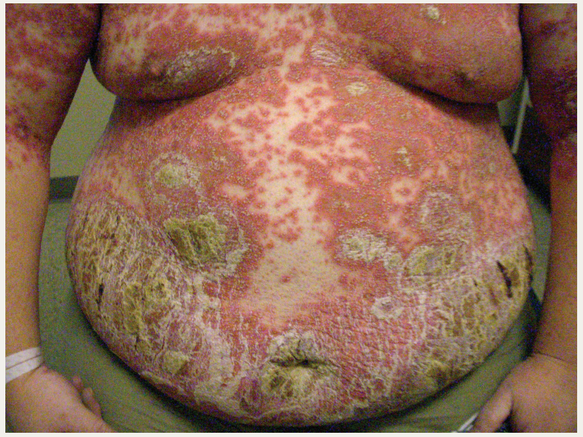

Figure 1. Erythroderma with multiple pustules

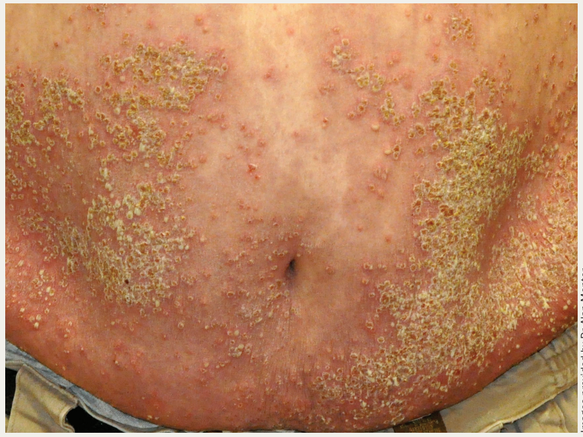

Figure 2. Close up of erythroderma with multiple pustules.

Images provided by Dr Alan Menter

Unmet needs

Limited literature notwithstanding, GPP clearly carries an outsize burden. One study in GPP patients reported an average Dermatology Life Quality Index (DLQI) score of 12.4, indicating severe impairment.[3] A comparison with plaque psoriasis revealed a DLQI score nearly 4 times higher in patients with a GPP flare. Studies of the economic burden show that patients with GPP have more comorbidities than those with plaque psoriasis and require more intensive care.[6] The medication burden for both dermatologic symptoms and comorbidities far exceeds that for plaque psoriasis. Available data suggest that patients with GPP experience at least one flare resulting in a hospitalization every 1 to 5 years.[7] Across the three data sets, the duration of hospitalization was about 10 to 14 days.[3]

In the survey of dermatologists cited earlier, most dermatologists suggested that available treatment options for flares of GPP are effective most (79%) or all (14%) of the time—but 38% noted that it was at least somewhat common for a flare to require hospitalization.[4] Nearly 75% reported that available medications were too slow to control flares, and two-thirds indicated that treatments did not adequately prevent new flares at least some of the time.

Treatment for GPP often follows the existing guidance for plaque psoriasis. For plaque psoriasis, targeted therapies have had a profound effect on treatment in recent years, but no targeted treatments are available for GPP. Ideal therapeutic agents would have a rapid onset of action, a rapid time to achieve disease clearance, the ability to prevent acute flares, and a favorable safety profile; such therapies should be readily accessible via approval or listing on formularies.[2]

Thus, there are key weaknesses in the current clinical management of GPP.[2] First, despite the publication in 2019 of psoriasis guidelines from the American Academy of Dermatology and the National Psoriasis Foundation, guidance for GPP is missing. Second, the current choice of treatments for GPP is limited and, as stated earlier, the options available generally follow what is used for plaque psoriasis. There is a profound need for therapeutic agents for GPP to be licensed in the United States and Europe, as are now available in Japan.

Future research should include potential differential treatment responses between ethnic groups to current and novel therapies as they become approved and available in different regions. Further, solid efficacy data to guide treatment choices in GPP are also lacking; this applies to both conventional agents and newer therapies such as biologics.

The immunologic pathogenesis: IL-36Ra and GPP

Although the first case of GPP was reported in 1910, its etiology and detailed pathogenesis have been only recently described. GPP is now known to be an autoinflammatory disease resulting from excessive expression of IL-1 family proteins in the skin and disinhibition of the signaling pathway that these proteins activate.

Marrakchi and colleagues reported that nine familial Tunisian patients with GPP carried the c.80T>C (p.Leu27Pro) homozygous missense mutation, *IL36RN*, which determines increased keratinocyte expression of the inflammatory cytokines in patients with GPP, such as IL-8, IL-36α, IL-36β, and IL-36γ. Therefore, *IL36RN* was identified as a causative gene for GPP and the disease caused by IL-36Ra decrease was defined as deficiency of IL-36 receptor antagonist (DITRA).[1]

Despite the importance of the IL-36 pathway, only 37% of dermatologists recognize that it is central to the pathophysiologic and clinical presentation of GPP.

The identification of loss-of-function mutations in *IL36RN* gene emphasizes the key role of this pathway in the pathogenesis of GPP. In recent years, several allelic variations and mutations in *IL36RN*, *CARD14*, *AP1S3* genes, as well as in the recently identified pathogenic myeloperoxidase (MPO) gene, have been found to be associated with GPP.[8] Among those genes, *IL36RN* mutations are the most common genetic abnormality, *CARD14* mutations are primarily present in GPP with plaque psoriasis and rarely in GPP alone. The pathogenic variants of *AP1S3* were mainly found in individuals of European origin and rarely in East Asians.

Evidence of the correlation between genotype and clinical phenotype of GPP characterized by various studies suggest that GPP is a heterogeneous disease with distinct clinical manifestations and genetic characteristics and requires a separate diagnosis and treatment.

References

1. Marrakchi S, Guigue P, Renshaw BR, et al. Interleukin-36–receptor antagonist deficiency and generalized pustular psoriasis. *N Engl J Med.* 2011;365(7):620-628.
2. Gooderham JM, Van Voorhees AS, Lebwohl MG. An update on generalized pustular psoriasis. *Exp Rev Clin Immunol.* 2019;15(9):907-919.
3. Kharawala S, Golembesky AK, Bohn RL, Esser D. The clinical, humanistic, and economic burden of generalized pustular psoriasis: a structured review. *Exp Rev Clin Immunol.* 2020;16(3):239-252.
4. Strober B, Kotowsky N, Medeiros R, et al. Unmet medical needs in the treatment and management of generalized pustular psoriasis flares: evidence from a survey of Corrona registry dermatologists. *Dermatol Ther (Heidelb).* 2021;11(2):529-541.
5. Ly K, Beck KM, Smith MP, Thibodeaux Q, Bhutani T. Diagnosis and screening of patients with generalized pustular psoriasis. *Psoriasis Targets Ther.* 2019;9:37-42.
6. Kotowsky N, Garry EM, Valdecantos WC, Gao R, Golembesky AK. Characteristics of generalized pustular psoriasis (GPP) patients: results from the Optum® Clinformatics™ Data Mart database. Abstract presented at: 2020 NORD Annual Meeting; October 8-9, 2020; Washington, DC.
7. Hanna ML, Singer D, Valdecantos WC. Economic burden of generalized pustular psoriasis and palmoplantar pustulosis in the United States. *Curr Med Res Opin.* 2021;37(5):735-742.
8. Zhou J, Luo Q, Cheng Y, Wen X, Liu J. An update on genetic basis of generalized pustular psoriasis (review). *Int J Mol Med.* 2021;47(6):118.