SKIN

BRIEF ARTICLE

New Onset Generalized Pustular Psoriasis Rapidly Improved with IL-36 Blockade

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ABSTRACT

Generalized pustular psoriasis is a relatively rare variant of psoriasis characterized by diffuse eruption of sterile pustules on an erythematous background. Untreated flares can result in life-threatening complications including sepsis and organ failure. Generalized pustular psoriasis has historically proven challenging to treat with an unpredictable clinical course and paucity of reliably efficacious treatment options. Until recently, there have been no FDA-approved therapies for generalized pustular psoriasis in the United States. In September 2022, the IL-36 receptor antagonist spesolimab became the first FDA-approved treatment for generalized pustular psoriasis in adults. We present a case of generalized pustular psoriasis with complete and rapid response to spesolimab.

INTRODUCTION

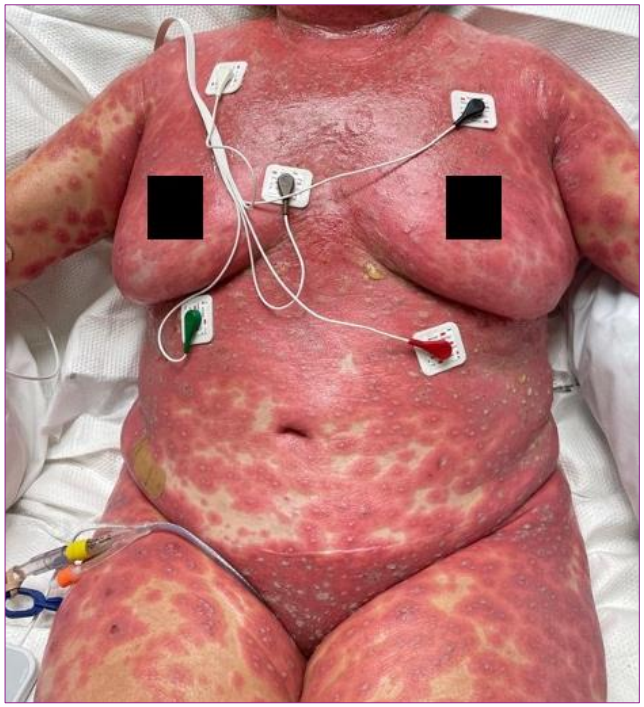
Generalized pustular psoriasis is an uncommon variant of psoriasis characterized by diffuse eruption of sterile pustules with potential for sepsis and organ failure. A paucity of reliably efficacious therapeutics has made this condition difficult to treat. Interleukin-36 (IL-36) receptor antagonists are emerging as a promising therapy for pustular psoriasis providing rapid and efficacious response. We present a case of generalized pustular psoriasis with complete response to spesolimab, an IL-36 receptor antagonist monoclonal antibody that recently became the first FDA-approved therapy for this condition. Physicians should be familiar with this now treatable disorder.

CASE REPORT

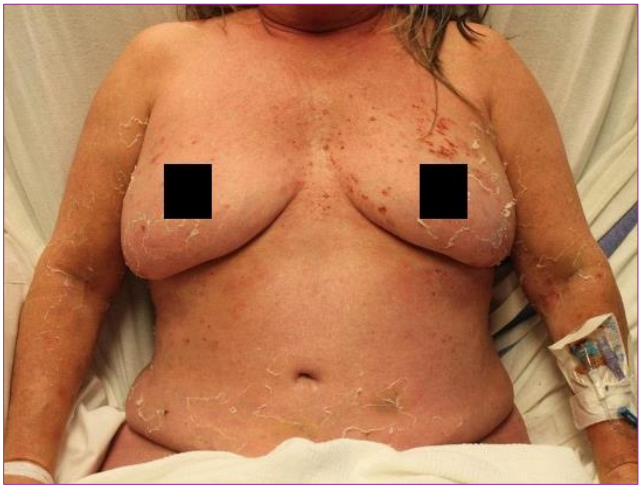
A 60-year-old female with past medical history of plaque psoriasis and psoriatic arthritis treated with guselkumab 100mg every 8 weeks presented to the emergency department with an acute generalized pustular dermatosis that developed after she received intramuscular triamcinolone and oral methylprednisolone to treat a presumable morbilliform drug eruption that developed after she was given oral clindamycin for paronychia. Both her cutaneous and articular disease had been well-controlled on guselkumab since February 2021 with minimal localized cutaneous disease after failing therapy with adalimumab, etanercept, ustekinumab,

secukinumab, and ixekizumab. The patient had rapid generalization of her skin lesions with severe skin tenderness, fever of 103.9°F, chills, tachycardia, and leukocytosis. She was admitted to the intensive care unit.

Physical examination was notable for diffuse coalescing and isolated pustules within a background of erythema involving the face, neck, trunk, groin, upper extremities, and lower extremities. There was significant edema of the face, trunk, and extremities. Two 4mm punch biopsies were performed from the left abdomen and left thigh. Histologic sections demonstrated subcorneal and intraepidermal spongiform pustules consistent with pustular psoriasis.



The patient was treated with a single intravenous infusion of spesolimab 900mg in addition to triamcinolone 0.1% ointment and hydrocortisone 1% cream. She had rapid and remarkable improvement within 18 hours of receiving spesolimab with almost complete resolution of superficial pustules and background erythema on the face, neck, trunk, and extremities. Physical examination 40 hours following spesolimab treatment showed continued improvement with complete resolution of all remaining pustules. The infusion was well-tolerated, and the patient reported no adverse effects. She was discharged home two days post-infusion with a plan for 1 month follow-up in outpatient dermatology clinic, continuation of topical treatment, and continuation of guselkumab.



DISCUSSION

Generalized pustular psoriasis is a relatively rare and potentially fatal autoinflammatory dermatologic condition with marked impacts on patient quality of life. Acute generalized pustular psoriasis commonly presents with accompanying systemic symptoms including fever, chills, malaise, and severe pain due to underlying systemic inflammation. Untreated flares can result in life threatening complications including sepsis, renal failure, hepatic failure, and cardiorespiratory failure.[1] Corticosteroid use and withdrawal is a known trigger for generalized pustular psoriasis flares, and other potential triggers include smoking, pregnancy, stress, infections, lithium, TNF-alpha inhibitors, and nonsteroidal anti-inflammatory drugs.[2,3,4]

While the immunopathogenesis involved in the development of generalized pustular psoriasis is complex, studies have identified the IL-36 pathway as a key element in the pathogenesis of this disorder.[2] Overexpression of IL-36, or a loss-of-function mutation in the IL-36 receptor antagonist IL-36RA, leads to increased levels of proinflammatory mediators and activation of IL-36 receptors on skin cells.[5,6] IL-36, which belongs to the IL-1 superfamily of cytokines, is vital to the homeostasis of the innate immune system. These family members include several cytokines, receptors, and accessory proteins that, when disturbed, can result in inflammatory dermatoses such as psoriasis.[7] Activation of IL-1 cytokines with their receptors results in downstream action of nuclear factor kappa B, mitogen-activated protein kinases, and ultimately proinflammatory gene expression.[7] In pustular psoriasis, unbalanced production of IL-1 and IL-36 contribute to autoinflammation, innate immune system activation, and neutrophilic infiltration of the epidermis, which leads to the clinical presentation of sterile pustules within a background of erythema.[8]

Generalized pustular psoriasis has historically proven challenging to treat with an unpredictable clinical course characterized by persistent disease or intermittent relapsing flares. With previously available treatment options, a quarter of patients experience persistent pustular lesions despite systemic therapy.[1] Because of the severity of this disease and risk of sepsis and end-organ dysfunction, flares are generally managed in the inpatient setting with a 10 day average length of admission.[1,2] Until recently, there have been no approved therapies for generalized pustular psoriasis in the United States with a paucity of evidence-based treatment options. Medical management of the disease has included the use of cyclosporine, systemic retinoids, methotrexate, and biologic agents.[9] However, these treatments are often far less effective for pustular psoriasis compared to standard plaque psoriasis and can be associated with a multitude of adverse effects including hypertension, renal toxicity, and teratogenicity.[10]

In September 2022, the IL-36 receptor antagonist spesolimab became the first FDA-approved treatment for generalized pustular psoriasis in adults. Spesolimab is a humanized monoclonal antibody that blocks the IL-36 receptor, thus inhibiting the ability of IL-36 to bind and initiate proinflammatory cascades.[10] While the exact impact of reduced IL-36 receptor activity in generalized pustular psoriasis is undetermined, rapid and sustained improvement in clinical symptoms and inflammatory markers including C-reactive protein was demonstrated in Effisayil phase 1 and 2 trials examining the efficacy of spesolimab.[11,12] Dosing of spesolimab in the treatment of generalized pustular psoriasis for adults is one 900mg intravenous infusion, then an additional 900mg infusion may be given one week later if the flare persists.[12] Imsidolimab is another IL-36 receptor antagonist that is currently in phase 3 trials and has shown promising results for the treatment of pustular psoriasis.[8]

CONCLUSION

Generalized pustular psoriasis should be considered in the differential diagnosis of any generalized pustular eruption. Because of associated fever and systemic symptoms and the pustular nature of the disease, generalized pustular psoriasis is often misdiagnosed as an infectious disorder. Primary care physicians, hospitalists, and emergency medicine physicians, who are

often seeing these patients at time of initial presentation, should be familiar with this now treatable disorder. This case highlights the potential of IL-36 inhibitors to improve morbidity and mortality and shorten the duration of hospital admissions for patients with generalized pustular psoriasis. By targeting proinflammatory cytokines involved in the development of generalized pustular psoriasis, this emerging therapeutic provides rapid and effective response with less toxicity than existing therapies.

Conflict of Interest Disclosures: BE disclosures include: Clinical Research Support-research funding to University: Abbvie, Anaptys-Bio, Boehringer Ingelheim, Bristol Myers Squibb (BMS), Celgene, Incyte, Leo, Lilly, Merck, Menlo, Novartis, Pfizer, Regeneron, UCB, Sun, Valeant (Ortho dermatology), Vanda; Consultant-received honorarium: Amgen, Arcutis, Boehringer Ingelheim, BMS, Celgene, Leo, Lilly, Novartis, UCB, Valeant (Ortho dermatology). All other authors declare no conflicts of interest.

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