

BRIEF ARTICLES

Generalized Pustular Psoriasis in an Adolescent Treated with Cyclosporine: A Diagnostic and Therapeutic Challenge

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ABSTRACT

Generalized pustular psoriasis (GPP) is rare in the pediatric population, accounting for only 0.5-0.6% of psoriasis cases in children. This presents a diagnostic and therapeutic challenge; biopsy is often required to differentiate GPP from similar entities such as acute generalized exanthematous pustulosis. We describe a case of GPP in a 15-year-old male presenting with widespread pustules, fever, and vital instability. The clinical presentation and biopsy results were consistent with a diagnosis of GPP. The patient was successfully treated with cyclosporine 3mg/kg/day. He was subsequently transitioned to 25 mg acitretin daily and remained in remission at the 9-month follow-up. We report this case to highlight available treatment options for GPP in the pediatric population and to underscore key clinical and histologic findings, which may aid dermatologists in proper diagnosis of this rare childhood disease.

INTRODUCTION

Generalized pustular psoriasis (GPP) is an uncommon and life-threatening variant of psoriasis that presents as an acute or chronic pustular eruption. GPP is especially rare in children and adolescents, accounting for only 0.5-0.6% of psoriasis cases in the pediatric population.¹ The safety and efficacy of treatments in this age group is not well established, though case reports describe safe use of oral retinoids, methotrexate, and phototherapy.² Here we present the use of cyclosporine to treat GPP in an adolescent without adverse events. Furthermore, we highlight clinical and

histological features that can aid in the diagnosis of this rare childhood disease.

CASE REPORT

A 15-year-old male with a past medical history significant for asthma and atopic dermatitis presented to the emergency room with a four-day history of rash, fever, and joint pain. He also reported a history of nausea and diarrhea 2 weeks prior to the onset of rash and fever.

On examination he was noted to have conjunctival erythema, palatal petechiae, and pinpoint pustules on an erythematous

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base on his neck, abdomen, and upper and lower extremities (Figure 1 and 2). Nikolsky sign was negative, though he reported burning of the eyes and extremities.

Vitals were significant for tachycardia to 103 beats per minute, hypotension to 100/49 mmHg, and fever to 101.3 °F. Laboratory results were notable for a leukocytosis to 13.4/mm³ (4,500-11,000/mm³) with 74% polymorphous nuclear cells (54-62%) and an albumin of 2.9 g/dL (3.5-5.5 g/dL). Liver function tests, calcium level, and ESR were normal. A rapid strep test was negative.

The differential diagnosis included acute generalized exanthematous pustulosis (AGEP), generalized pustular psoriasis, deficiency of the IL-36R antagonist (DITRA), and linear IgA bullous disease. Punch biopsies from the trunk and lower extremities demonstrated regular acanthosis and subcorneal pustules within the spinous layers of the epidermis with a diminished granular layer. The stratum corneum showed focal mounds of parakeratosis with neutrophils, mild spongiosis, and subcorneal pustules. The suprapapillary plates were attenuated. No eosinophils were noted. Small, ectatic capillaries were present in the dermal papillae (Figure 3a and 3b). Direct immunofluorescence was negative.

Clinical and histologic findings were most consistent with GPP. Cyclosporine 3mg/kg/day was initiated and the patient's lesions began to desquamate the following day. As an outpatient, he was transitioned to acitretin 25mg daily and has been maintained on this for the past 9 months without any recurrence.

Figure 1. Clinical presentation of left lower extremity on hospital day 1. Physical exam was notable for pinpoint pustules coalescing in some areas into larger pustular bulla on a background of erythema on neck, trunk and upper and lower extremities.



SKIN

Figure 2. Clinical presentation of left lower extremity on hospital day 2. On day 2, the pustules became more confluent to form pustular lakes on the hands and lower extremities (Figure 2), Note the worsening pustular lesions that have enlarged and become more confluent in addition to pustular lake formation on the left lower extremity.



Figure 3a. Hematoxylin and eosin, 10x; At low power the epidermis shows regular acanthosis and subcorneal pustules within the spinous layers. The granular layer is reduced.

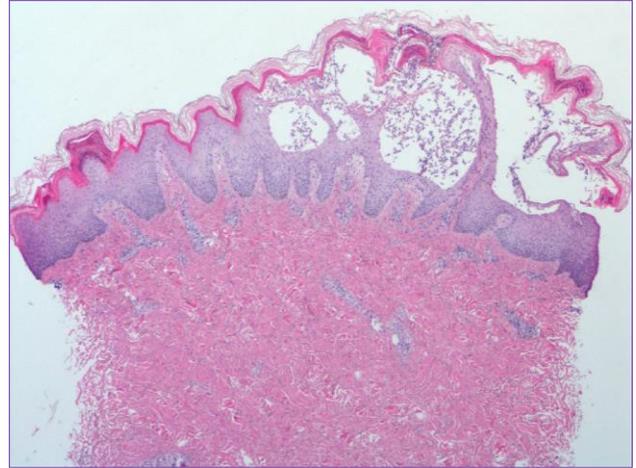
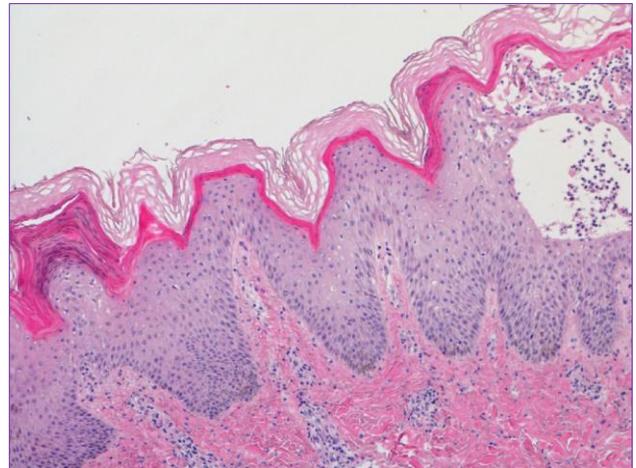


Figure 3b. Hematoxylin and eosin, 40x; The stratum corneum shows focal mounds of parakeratosis with neutrophils. Mild spongiosis and subcorneal pustules are also present. The suprapapillary plates are attenuated and the stratum corneum shows focal parakeratotic scale with neutrophils. Small, ectatic capillaries are present in the dermal papillae.



DISCUSSION

GPP, also known as von Zumbusch psoriasis, is a rare but severe form of psoriasis. GPP is a multi-system disease, consisting of the sudden onset of sterile pustules and erythema often accompanied by fever, malaise, erythroderma, asthenia, myalgia, and arthralgia. Life-threatening complications include sepsis, renal failure, neutrophilic cholangitis resulting in hepatic failure, respiratory distress secondary to neutrophilic pneumonitis, congestive heart failure, and death.³ Lab abnormalities include an elevated C-reactive protein level, hypocalcemia, hyperleukocytosis with neutrophilia, and elevated liver function tests.³

Epidemiologic studies suggest that GPP is rare in the general population. It typically occurs in patients already diagnosed with chronic plaque psoriasis, though it can be the initial presentation of psoriasis as in our patient.⁴ Moreover, GPP is exceedingly rare in children. A review of 1,262 pediatric psoriasis patients found that GPP accounted for only 0.6% of cases.¹ Known triggers of GPP include hypocalcemia, rapid steroid tapers, pregnancy, and infections.⁵ One study suggested that upper respiratory infection was the most commonly implicated trigger for GPP.⁶ Of note, our patient reported a recent history of gastroenteritis, which may have been his trigger. Medications associated with GPP flares include minocycline, terbinafine, acetazolamide, hydroxychloroquine, acetazolamide, and salicylates.⁴

The pathogenesis of pustular psoriasis is not fully known, yet advances in genetics have elucidated the role of three genes in its development. An autosomal recessive pattern mutation in the IL-36 receptor

antagonist, located on chromosome 2q13-q14 was associated with GPP. It is speculated that such a mutation may lead to unregulated secretion of pro-inflammatory cytokines including IL-1 and NF- κ B.⁷ A de novo gain of function mutation in the caspase CARD-14 gene was also identified in a case of childhood GPP.⁸ This mutation is hypothesized to activate NF- κ B and subsequently increase production of the pro-inflammatory cytokines IL-8 and IL-36. Of note, patients with the CARD-14 mutation tend to have a severe form of disease that is often refractory to treatment.⁸

Histologically, pustular psoriasis is characterized by neutrophils migrating from the papillary capillaries into the stratum corneum of the epidermis. Aggregates of neutrophils, called spongiform pustules of Kogoj, accumulate between degenerated and flattened keratinocytes in the upper malpighian layer of the epidermis to form subcorneal macropustules.⁹

The most important differential diagnosis is acute generalized exanthematous pustulosis (AGEP). Great care must be taken to distinguish the two as management differs. AGEP typically presents as acute, non-follicular pustules on an erythematous base, often after ingestion of a new medication, usually antibiotics. Key clinical differences between AGEP and GPP include shorter duration of fever and pustules in AGEP (9.4 \pm 4.6 days in AGEP compared to 37 \pm 20 days) and spontaneous resolution of symptoms for AGEP but not GPP.¹⁰ Histologically, GPP can be distinguished from AGEP by relative lack of eosinophils and necrotic keratinocytes, and presence of tortuous or dilated blood vessels.⁹

Treatment of GPP in the pediatric population is not well studied. Based on case reports, acute GPP has been safely treated with

systemic therapies such as methotrexate, oral retinoids, and phototherapy.² Acitretin is often used as the first-line therapy for long-term management, though care must be taken when using this medication in adolescent females due to teratogenicity. Few case reports, including the current one, describe use of low-dose cyclosporine to treat acute GPP in children.¹¹ Biologics such as etanercept, adalimumab, and infliximab have been shown to induce remission safely in children as well.¹²

CONCLUSION

In summary, we report the case of pediatric patient safely treated with cyclosporine for GPP. Given the rarity of GPP in the pediatric population, large cohort studies are necessary to establish best practices in histological diagnosis of GPP compared to other clinically similar lesions, while also establishing treatment safety and efficacy in this particular patient population.

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