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CASE REPORT

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A Rare Case of Acute Generalized Exanthematous Pustulosis in a Filipino Female Pediatric Patient with Systemic Lupus Erythematosus*

Manuel V. Mendoza, Jr., MD, MBA, Maritess P. Macaraeg, MD, Camelia Faye R. Tuazon, MD

Department of Dermatology, Region 1 Medical Center, Dagupan City, Pangasinan, Philippines

Correspondence to:
Manuel V. Mendoza, MD, MBA
Department of Dermatology
Region 1 Medical Center,
Arellano St., Dagupan City, 2400
Pangasinan, Philippines
E-mail: mendozawel@gmail.com
ORCiD: https://orcid.org/0009-0002-6686-8833

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ABSTRACT

Acute generalized exanthematous pustulosis (AGEP) is a rare, febrile drug eruption characterized by non-follicular pustules and systemic involvement. Its features may overlap with systemic lupus erythematosus (SLE), complicating diagnosis and management. This study reports the first documented pediatric case of this complex disease phenomenon.

An 18-year-old Filipino female with newly diagnosed SLE on hydroxychloroquine presented with diffuse non-follicular pustules and fever after the initiation of azithromycin for upper respiratory tract infection. Histopathology examination revealed subcorneal pustules, which, together with clinical and dermoscopic findings, supported the clinical diagnosis of Definitive AGEP (EuroSCAR Score 11). Both identified high-risk drugs, hydroxychloroquine and azithromycin, were discontinued. Following drug withdrawal, corticosteroid, and supportive care, her clinical condition subsequently improved.

This report highlights the diagnostic challenge between AGEP and SLE. An interleukin-8-mediated mechanism appears to play a central role in bridging the pathogenesis of both conditions. Despite controversies, corticosteroids have proven to be an effective adjunct in the management of AGEP, while controlling the underlying SLE.

Keywords: acute generalized exanthematous pustulosis, systemic lupus erythematosus, acute generalized exanthematous pustulosis in systemic lupus erythematosus, AGEP, SLE

INTRODUCTION

Acute generalized exanthematous pustulosis (AGEP) is a cutaneous drug eruption characterized by the rapid development of pustules initially seen on the intertriginous area and the trunk.[1] There are no local statistics available because AGEP is rare, with an incidence rate of 1-5/1,000,000 cases annually.[1-3] It is commonly caused by drugs like beta-lactams, macrolides, and anticonvulsants.[1,2] Within 2-10 days of exposure, AGEP will manifest as generalized pustules, accompanied by fever, leukocytosis, and neutrophilia, with hepatic and renal involvement in approximately 20% of cases.[1]

Systemic lupus erythematosus (SLE) is a chronic, multisystemic autoimmune disease with the hallmark of autoantibody production and generation of immune complexes, triggering an inflammatory response leading to tissue injury. SLE can present with various cutaneous findings, including a butterfly rash, photosensitivity, annular lesions, and alopecia.[1] The pustular manifestation of AGEP and SLE presents a key diagnostic dilemma in evaluating drug eruption in patients with SLE.

The prevalence of SLE in the Asia-Pacific Region ranges from 4.3 to 45.3 cases per 100,000 people.[4] However, there is still no published data that specifically addresses the incidence and prevalence of AGEP in patients with SLE. Notably, Sequeira et al. reported a 38% prevalence of drug reactions in SLE patients, emphasizing their susceptibility to adverse drug eruptions.[5-7] This case further underscores this unexplored interplay between drug eruption, especially AGEP, and SLE.

Table 1. Systemic lupus erythematosus signs and symptoms

Systemic lupus erythematosus diagnosis*	
Malar Rash	Present
Photosensitivity	Present
Oral ulcers	Present
Serositis	Whole abdominal ultrasound noted minimal acites and incidental findings of Bilateral Pleural effusion
Immunologic disorder (Anti-DsDNA)	374.03 IU/mL (Strongly positive)
Anti-nuclear antibody	1:640 (Significantly positive)

**Eight weeks prior to dermatologic referral, the patient presented with a constellation of signs and symptoms, consistent with SLE.*

To the extent of our knowledge, this is the first documented case of AGEP in a pediatric Filipino with SLE. This study aims to describe the clinical presentation, diagnostic challenges, interactions between AGEP and SLE, potential supplemental tests, and successful management of this complex case in the context of pediatric SLE, thereby contributing to the existing limited literature.

CASE

An 18-year-old Filipino female patient, diagnosed with SLE (Table 1 presented previous signs and symptoms eight weeks prior) on hydroxychloroquine as maintenance, was referred to our dermatology services for pustules. Initially, the patient was admitted under pediatric services for an upper respiratory tract infection and was given azithromycin 500 mg.

On the second day of admission, the patient developed multiple non-follicular, monomorphic pustules on the back and axilla (Figure 1A), accompanied by fever (maximum temperature of 39°C). The patient was also on Day 54 of hydroxychloroquine therapy and Day 2 of azithromycin therapy. There was no mucosal, genital, hair, or nail involvement.

The timeline of high-risk drugs is outlined in Table 2. The patient had a personal and family history of hypertension, with no personal and familial history of autoimmune disease, atopy, or allergy. The personal-social and obstetric-gynecological history was unremarkable.

Physical examination revealed multiple, non-follicular, monomorphic pustules on erythematous bases on the axilla, trunk, and extremities. The patient was alert, awake, and coherent with no hallucinations and personality changes. She was also hypertensive at 130/80 mmHg. The rest of the physical exam was unremarkable.

Laboratory tests during this current admission highlighted leukocytosis, neutrophilia, microcytic, hypochromic anemia, and thrombocytopenia in complete blood count and peripheral blood smear. Urinalysis revealed hematuria and proteinuria. No organism was also noted in the Gram and KOH Stain.

Table 2. High-risk drug timeline

Drugs	2 mo. PTA Malar Rash, Fever	1 mo. PTA No skin lesions	7 d PTA Papules	1 d PTA Ad Plaques	D2 Ad Pustules	D 12 Ad Resolved
HCQ						
AZT						

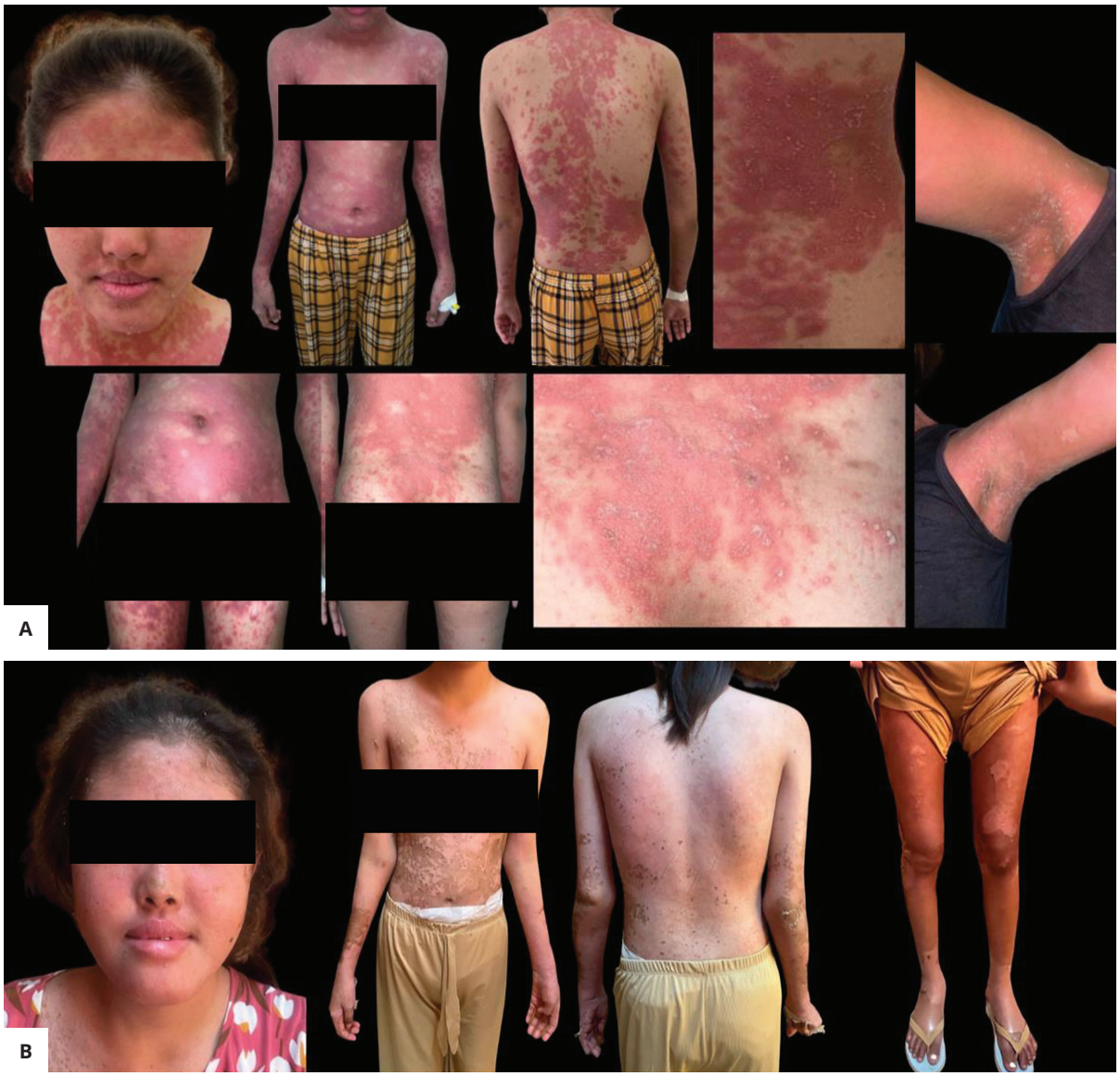

Figure 1. **(A)** The patient presented non-follicular, monomorphic, pustules on the back and axilla at day 2 Azithromycin and day 54 of Hydroxychloroquine. **(B)** There is noted desquamation and resolution of pustules after discontinuing azithromycin for 10 days and hydroxychloroquine for 12 days.

A 4-mm skin punch biopsy was performed on the right arm, which showed subcorneal collection of neutrophils (Figure 2B). Other histopathologic findings include moderate spongiosis, papillary edema, and limited to superficial perivascular infiltration. On light dermoscopy, there are yellow-white globules on an erythematous background. Clinicopathologic and dermoscopic findings supported the diagnosis of acute generalized exanthematous pustulosis, likely secondary to hydroxychloroquine vs. azithromycin (Table 3, EuroSCAR Score: 11 – definitive AGEP).[2,3,8]

Management involved the identification and prompt withdrawal of identified drug triggers. Azithromycin and hydroxychloroquine were immediately discontinued. Hydrocortisone 100 mg IV TID (1.8 mg/kg/day prednisone equivalent) was administered for 10 days. Supplementation with sandwich dressing – comprising mupirocin 2% ointment, gauze in a saline solution, and petroleum jelly impregnated gauze – was also provided. Significant improvement was observed, leading to subsequent discharge (Figure 2B).

On follow-up via telemedicine after one month, complete resolution of cutaneous lesions was reported. Due to logistical and financial constraints, a physical follow-up could not be conducted. Consequently, rechallenge tests and other supplemental tests were not feasible.

Table 3. AGEP validation score from the EuroSCAR study group *(reproduced with permission from Dr. Mockenhaupt)* [2,3]

	Score	Description
Morphology		
Pustules	+2	Typical, non-follicular
Erythema	+2	Typical, diffuse
Distribution	+2	Compatible, trunk and members
Post-pustular Desquamation	+1	Yes
Mucosal Involvement	0	No
Onset		
Acute Onset	0	<10 days
Resolution	0	<15 days
Fever	+1	>38.75°C
Polymorphonuclear Neutrophils	+1	>7000 cells/mm^3
Histopathologic Analysis	+2	Subcorneal Pustules
Total	**11**	Definitive AGEP

Interpretation: No AGEP (<0), possible AGEP (1-4), probable AGEP (5-7), and definitive AGEP (8-12).

DISCUSSION

This case highlighted the overlapping presentations of AGEP and SLE, which pose a significant diagnostic dilemma and delay the timely diagnosis of drug eruptions. A review of underlying mechanisms revealed that immune dysregulation and chemokine hyperactivity, particularly interleukin-8 (IL-8), were key features of both conditions. In SLE, the loss of tolerance leads to autoantibody production, immune complex deposition, and immune complex activation, all of which contribute to increased IL-8 levels.[1,9]

While AGEP, a delayed drug-induced hypersensitivity reaction, activates T-cells, which in turn release IL-8, triggering the recruitment of neutrophils and resulting in the formation of diffuse sterile pustules.[1,10] This shared IL-8-driven pathway may account for the enhanced susceptibility of SLE patients to drug eruptions, particularly AGEP.

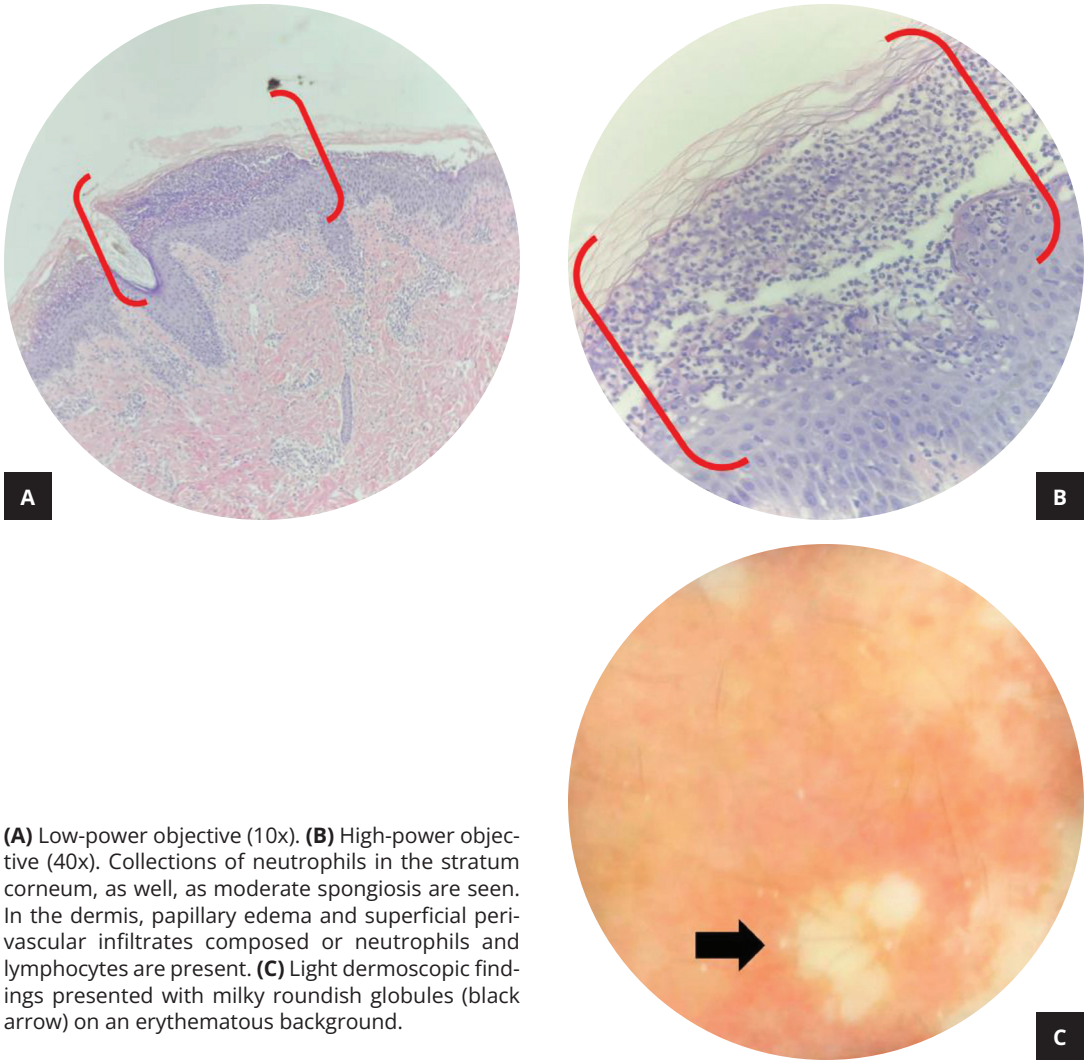

Figure 2. **(A)** Low-power objective (10x). **(B)** High-power objective (40x). Collections of neutrophils in the stratum corneum, as well, as moderate spongiosis are seen. In the dermis, papillary edema and superficial perivascular infiltrates composed or neutrophils and lymphocytes are present. **(C)** Light dermoscopic findings presented with milky roundish globules (black arrow) on an erythematous background.

The histopathologic examination revealed the key finding of subcorneal collection of neutrophils, which is characteristic of AGEP.[1] Notably, the biopsy report did not demonstrate key findings typical of cutaneous lupus, like superficial and deep lymphocytic perivascular dermatitis, interface vacuolar dermatitis, follicular plugging, and increased dermal mucin deposition.[1] Furthermore, the absence of parakeratosis, psoriasiform hyperplasia, Munro microabscesses, Auspitz sign, and nail findings ruled out pustular psoriasis.[1] Other laboratory tests, including Gram stain, KOH stain, and skin cultures, showed the absence of organisms, effectively excluding infectious causes of pustulosis like bullous impetigo and tinea infection.[1]

This case involved exposure to two high-risk AGEP drug triggers, azithromycin and hydroxychloroquine. In particular, azithromycin with a half-life of up to 60 hours [11] was associated with an increased risk of AGEP [Odds ratio (OR) = 11, 95% CI 2.7-48).[2] In contrast, hydroxychloroquine has an exceptionally long half-life (up to 50 days), and delayed-onset AGEP cases have been reported up to 122 days after initiation [12] with significantly increased risk of AGEP with hydroxychloroquine (OR = 39, 95% CI 8-191).[2]

Drug rechallenge was not performed due to logistical considerations. Despite this, the EuroSCAR score and the clinical course strongly supported the diagnosis of AGEP. Despite its variable sensitivity of up to 75%,[13] patch testing remains a valuable alternative diagnostic tool – offering a safer and practical option in confirming drug causality, especially when drug rechallenge is not feasible.

The Region 1 Medical Center – Department of Dermatology January 2023-January 2025 census noted a significantly increased likelihood of AGEP in patients with SLE (OR: 35)[14] when compared to other types of cutaneous adverse drug reactions (CADR). Despite the lack of published studies, these findings supported the potential intuitive and immunologic link between SLE and AGEP. This association was further described in Figure 3.

The limitations of current diagnostic tools and the lack of data were highlighted in this report. This emphasizes the need for further investigation into AGEP in patients with SLE to define the true incidence of AGEP in SLE cases, clarify the pathways involved, and explore regional variations in disease presentation and susceptibility.

The primary therapeutic approach of AGEP involved the identification, withdrawal, and avoidance of drug triggers. However, discontinuation of the drug may carry clinical implications, especially in this complex case. Macrolides, such as azithromycin, used as antibiotics, may be substituted with other appropriate antibacterial medications. However, discontinuing hydroxychloroquine is more critical, as it is a cornerstone in SLE management. Its withdrawal may increase the risk of disease flares. Therefore, patients should be closely monitored, and alternative immunosuppressive therapy should be prescribed to maintain disease control.[15]

The use of systemic corticosteroids in AGEP is controversial. However, it may still be warranted. The use of systemic corticosteroids is noted to decrease hospitalization days by up to 3 days.[16] With the SLE remaining stable, this highlights that the use of systemic steroids, when used judiciously, may be beneficial in cases of drug eruption with overlying autoimmune diseases. Individualized supportive

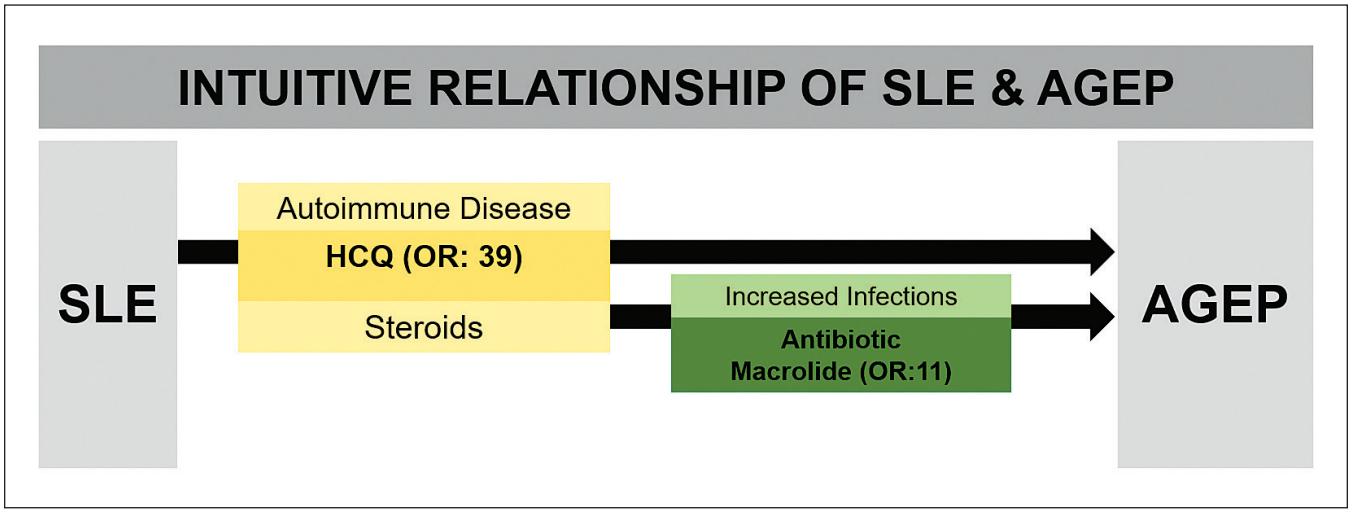

Figure 3. Intuitive relationship of SLE and AGEP. SLE treatment often involves immunomodulator like Hydroxychloroquine (HCQ) due to its availability and established efficacy. However, immunosuppressive effects of HCQ with steroids could predispose patients to infections requiring antibiotic use such as azithromycin. Notably, both HCQ and azithromycin are high-risk AGEP triggers.[2]

therapy, such as moist dressings and antihistamines, may also be provided to alleviate symptoms and was seen to improve comfort. While AGEP carries a favorable prognosis with a mortality rate of 2.5%,[17,18] this case demonstrated a consistent positive prognosis despite the complications introduced by underlying SLE.

CONCLUSION

This report highlights the complicated relationship between acute generalized exanthematous pustulosis and systemic lupus erythematosus. This complex clinical scenario, characterized by overlapping features of AGEP and SLE, necessitates meticulous clinicopathologic correlation and thorough exclusion of alternative diagnoses, including autoimmune diseases, other inflammatory dermatoses, and infectious etiologies.

The cornerstone of AGEP management remains early recognition and prompt discontinuation of the offending agents. Given the crucial role of hydroxychloroquine in SLE management, its discontinuation should warrant careful monitoring and substitution to prevent flare-ups and other systemic complications. The use of corticosteroids was demonstrated to be a safe and effective adjunct in AGEP management, while concurrently maintaining control of underlying SLE.

This report provided valuable insights into this rare and complex medical scenario. Further investigations are warranted to better explore this immunologic association between AGEP and SLE and to develop evidence-based protocols for patients with autoimmune conditions.

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Ethical Consideration
Patient consent form was obtained prior to submission of manuscript.

Statement of Authorship
All authors certified fulfillment of ICMJE authorship criteria.

Author Disclosure
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