DOI: htttps://doi.org/10.3126/njdvl.v23i1.69062

Unveiling Uncommon Etiologies of Acute Generalized Exanthematous Pustulosis – A Case Series

Irene Nirmala Thomas,[1] Sahana Begum Mohamed Sadiq,[1] Nithya Priyadharshini Shanmugam,[1] Arishta Bala,[1] Saranya Mohan[1]

[1]Department of Dermatology, Shri Sathya Sai Medical College and Research Institute, Ammapettai, Chengalpet, Tamil Nadu, India

Abstract

Acute Generalized Exanthematous Pustulosis (AGEP) is a rare, severe adverse cutaneous drug reaction characterized by fever and numerous sterile, non-follicular pustules on an erythematous base that manifests 2 to 14 days after drug exposure. While systemic antibiotics, particularly beta-lactams and macrolides, are frequently implicated, they can also be triggered by other drugs, including hydroxychloroquine, antifungals, antivirals, antineoplastics, and herbal remedies like Ginkgo biloba, curcumin, etc. This case series reports three unusual instances of AGEP after intake of tablet paracetamol, native medicines, and syrup azithromycin. All three patients met the EUROSCAR diagnostic criteria for AGEP, with scores indicating a definite diagnosis. Treatment included the withdrawal of the offending drug, symptomatic management, topical and systemic steroids, resulting in the resolution of lesions within a week. This series emphasizes the necessity of considering rare and less common etiologies, highlighting that drugs like paracetamol, native medicines, and azithromycin, while infrequently associated, can still provoke AGEP. Comprehensive evaluation of all possible triggers is crucial for accurate diagnosis and effective treatment.

Keywords: Azithromycin; Native medicines; Paracetamol

Introduction

Acute generalized exanthematous pustulosis (AGEP) is an acute febrile drug eruption with an incidence of one to five cases per million per year characterized by numerous, non-follicular sterile pustules on an erythematous base with neutrophilic leukocytosis. It occurs 2 to 14 days after initiation of the implicated drug.[1,2] Systemic antibiotics, especially beta-lactams, and macrolides, are the most frequently associated with AGEP. However, other reported causes include analgesics, hydroxychloroquine, antiviral, antiparasitic, antifungal medications, antirheumatic drugs, anticonvulsants, antineoplastic, and intravenous contrast agents.[3] Here, we describe a case series of three patients of AGEP with uncommon etiologies.

Case 1

A 31-year-old female was admitted with complaints of fever and rash. Apart from oral paracetamol for fever, there was no history of taking any other drug. On

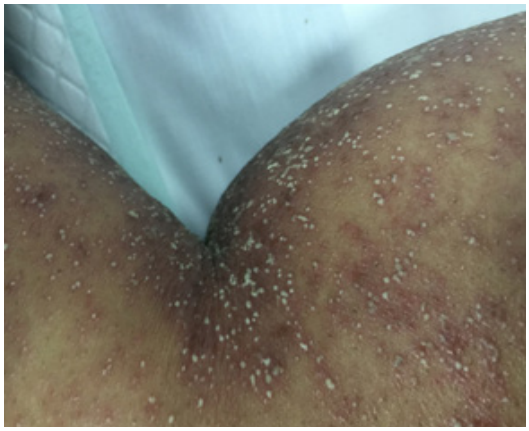

Figure 1.1: Non follicular pustules with erythema involving elbow

Funding: None
Conflict of Interest: None

Corresponding Author:
Dr. Nithya Priyadharshini Shanmugam
Department of Dermatology, Shri Sathya Sai Medical College and Research Institute Ammapettai, Chengalpet, Tamil Nadu, India
ORCID ID: 0000-0002-0565-8931
Email: nithi12.dr@gmail.com

Date of Submission: 23rd August 2024
Date of Acceptance: 25th December 2024
Date of Publication: 5th March 2025

How to cite this article

Thomas IN, Sadiq SBM, Shanmugam NP, Bala A, Mohan S. Unveiling Uncommon Etiologies of Acute Generalized Exanthematous Pustulosis – A Case Series. NJDVL. 2025; 23(1): 36-39. htttps://doi.org/10.3126/njdvl.v23i1.69062

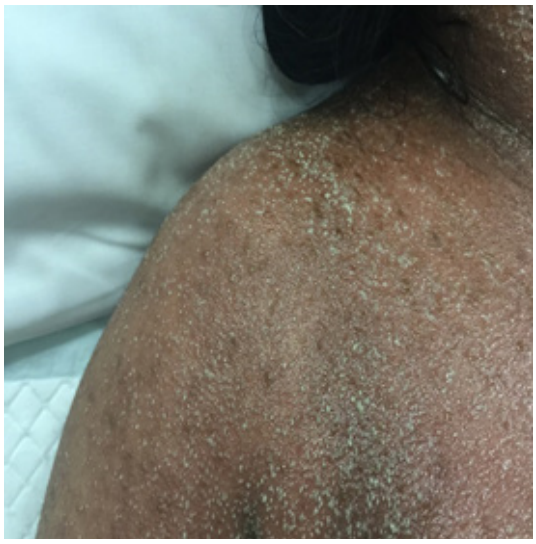

Figure 1.2: Non follicular pustules with erythema involving right shoulder and right arm

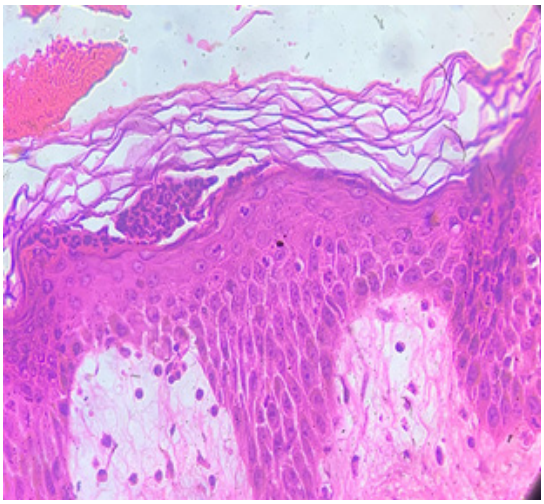

Figure 2.2: Diffuse epidermal spongiosis, sub corneal pustules filled with neutrophils (H&E stain, 40x)

examination, widespread erythema with hundreds of small, flaccid, confluent, non-follicular pustules along the groin and flexor surfaces were noticed. Routine laboratory test revealed an elevated neutrophil count of 27,000/mm3, CRP level was 118mg/L, and pus culture and sensitivity were negative. Skin biopsy was not performed because of financial limitations. Based on EUROSCAR diagnostic criteria with a score of 9 (Table 1), AGEP was diagnosed. Symptomatic oral and topical therapy was given. The rash resolved by the 5th day, and then the patient was discharged.

Case 2

A 29-year-old female presented with complaints of fever and rashes for 4 days after intake of native medications, which is a mixture of Phyllanthus emblica, Terminalia bellerica, and Terminalia chebula.

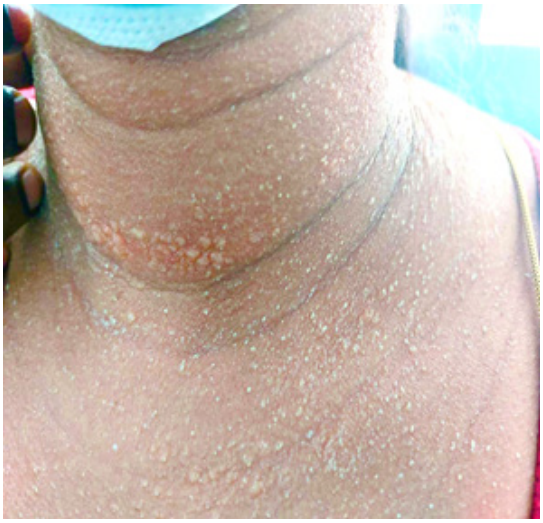

Figure 2.1: Numerous non-follicular pustules on erythematous bases over anterior aspect of neck

On physical examination, multiple well-defined skin-coloured papules and non-follicular pustules on the erythematous base were noticed all over the body, sparing the face, and multiple grouped vesicles to bulla were present over the extensor and flexor aspects of the wrist and forearm. Routine laboratory tests revealed elevated neutrophil count. Histopathological examination of skin biopsy revealed spongiosis, sub-corneal pustules filled with neutrophils and eosinophils, and papillary dermis showed edema and perivascular infiltration of neutrophils, eosinophils, and lymphocytes. With EUROSCAR diagnostic criteria AGEP score 12 (Table 1), a definite diagnosis of AGEP was made. Patient was managed symptomatically and also treated with topical steroids and emollients. Lesions resolved after a week with exfoliation.

Case 3

An 8-year-old boy was admitted with a history of rashes for 2 days after treatment with syrup azithromycin for

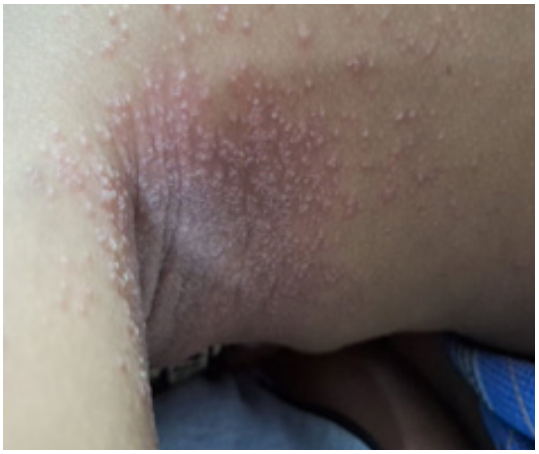

Figure 3.1: Numerous non-follicular pustules with erythema involving left axillary fold

Parameters	Case 1		Case 2		Case 3	
Pustules	Typical, non - follicular pustules	2	Typical, non - follicular pustules	2	Typical, non-follicular pustules	2
Erythema	Typical, widespread	2	Typical, diffuse	2	Typical, diffuse	2
Distribution	Typical, Generalized with flexural accentuation	2	Typical, involving all over the body sparing face	2	Typical, involving Peri-oral, peri-orbital, axilla, chest, genitals, and gluteal area	2
Post pustular desquamation	Yes	1	Yes	1	Yes	1
Fever	Yes	1	Yes	1	Yes	1
PMN count	27,000 / mm^3	1	16,000 / mm^3	1	-	-
Skin histology	-	-	Spongiosis, sub-corneal pustules filled with neutrophils and eosinophils, papillary dermis showed edema and perivascular infiltration of neutrophils, lymphocytes and eosinophils.	3	-	-
EuroSCAR AGEP validation score	9		12		8	

Table 1: Clinical and diagnostic findings of 3 patients according to EuroSCAR study group 2001

cold and throat pain. On physical examination, multiple non-follicular pustules and papules with erythema were noted over the periorbital and perioral area, axillary folds, chest, gluteal, and genitals sparing palms and soles. His EUROSCAR AGEP validation score was 8 (Table 1). Syrup azithromycin was withdrawn, and the patient was managed with a systemic steroid of dose 1mg/kg/day for 3 days and rapidly tapered to 10mg/day. After a week, the lesions were resolved, and was discharged.

Discussion

AGEP is a severe cutaneous drug reaction that predominantly affects females.[4] It is a T cell-mediated delayed type of hypersensitivity reaction. CXCL-8 is involved in the formation of pustules by neutrophilic recruitment.[5] AGEP typically presents with sudden onset of non-follicular sterile pustules on an erythematous base in response to the drug. The interval between the onset of symptoms and drug intake is short, from 2 hours to 4 weeks.[6] The distribution favours flexures. Mucous membrane involvement is rare. It is often associated with fever (>38˚C) and neutrophilic leukocytosis (neutrophils >7000/mm3). Histopathologically, AGEP is characterized by spongiosis of the epidermis and dermis, subcorneal and/or intraepidermal pustules with edema of the papillary dermis and dermal inflammatory infiltrates containing neutrophils and eosinophils. In some cases, leukocytoclastic vasculitis and necrotic keratinocytes are seen. EUROSCAR diagnostic criteria help to diagnose AGEP. A score between 1 to 4, 5 to 7, and 8 to 12 indicates a possible, probable, and definite diagnosis of AGEP, respectively.[1] AGEP is a self-limiting condition resolving by desquamation of pustules after withdrawal of offending drugs.

Drugs are responsible for 90% of cases of AGEP. Pristinamycin, quinolones, ampicillin/ amoxicillin, hydroxychloroquine, terbinafine, diltiazem, ketoconazole, and fluconazole have strong association with AGEP, while macrolides, oxicam, anti-epileptic, and non–steroidal anti-inflammatory drugs have weaker associations. AGEP can occur secondary to infections like Coxsackie B4, cytomegalovirus, and enterovirus.[5]

In this case series, all three patients fulfilled the diagnostic criteria for AGEP with scores of 8, 9, and 12. All three patients were managed symptomatically and with topical and systemic steroids, resulting in lesion resolution within a week. Our three patients had rare aetiologies associated with AGEP, such as paracetamol, native medication, and azithromycin.

Chitprapassorn Thienvibul et al., reported that 5.3% of AGEP cases were associated with natural herbs.7 AGEP induced by natural herbs have also been documented in Australia, Spain, and Tunisia.[8-11] The association of AGEP with natural herbs, although infrequent, is reported in various countries and should be considered, especially in populations where herbal remedies are widely used. Paracetamol, a frequently used over-the-

counter antipyretic, has been rarely associated with AGEP, with only a few documented cases.[12-14] Similarly, while azithromycin is a commonly prescribed antibiotic, its association with AGEP is uncommon and has been reported in only a limited number of cases.[15-17] Thus, azithromycin should also be considered a possible risk factor for AGEP.

Therefore, when assessing a patient with AGEP, when common causes are excluded, it is essential to consider the possibility of rarer aetiologies, as seen in our patients. An approach to patients with generalized pustular eruptions would be first to establish the diagnosis of AGEP using diagnostic criteria outlined by EUROSCAR. A detailed history regarding aetiology is essential to unravel rare causes that might be missed.

Conclusion

In summary, when treating patients with AGEP, it is important to look beyond antibiotics as the sole potential cause. This case series highlights the importance of considering a broad range of possible triggers for Acute Generalized Exanthematous Pustulosis (AGEP) beyond the commonly recognized aetiologies. Consideration should also be given to native medicines, commonly used paracetamol, and azithromycin, all of which can potentially trigger AGEP, emphasizing the need for a comprehensive evaluation of all possible causes. Clinicians should remain vigilant in assessing these less common triggers to ensure an accurate diagnosis and effective management of AGEP.

References

1. Sidoroff A, Halevy S, Bavinck JN, Vaillant L, Roujeau JC. Acute generalised exanthematous pustulosis (AGEP)–A clinical reaction pattern. J Cutan Pathol. 2001;28:113–9. https://doi.org/10.1034/j.1600-0560.2001.028003113.x
2. Shamloul G, McEldrew E, Kesty C, McClain R. Unique presentation and unusual cause of acute generalized exanthematous pustulosis: case report. J of Skin. 2023;7(1),598–601. https://doi.org/10.25251/skin.7.1.7
3. Moore MJ, Sathe NC, Ganipisetti VM. Acute generalized exanthematous pustulosis. 2023 May 3. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2024 Jan–. PMID: 37276304.
4. Tamir E, Wohl Y, Mashiah J, Brenner S. Acute generalized exanthematous pustulosis: a retrospective analysis showing a clear predilection for women. Skinmed. 2006;5(4): 186–8. https://doi.org/10.1111/j.1540-9740.2006.05019.x
5. Feldmeyer L, Heidemeyer K, Yawalkar N. Acute Generalized Exanthematous Pustulosis: Pathogenesis, Genetic Background, Clinical Variants and Therapy. Int J Mol Sci. 2016;17(8):1214. https://doi.org/10.3390/ijms17081214
6. Beltrana C, Vergier B, Doutre MS, Beylot C, Beylot-Barry M. Pustulose exanthématique aiguë généralisée induite par l'application d´Algipan®. Ann Dermatol Venereol. 2009;136(10): 709–12. https://doi.org/10.1016/j.annder.2008.10.042
7. Thienvibul C, Vachiramon V, Chanprapaph K. Five-Year Retrospective Review of Acute Generalized Exanthematous Pustulosis. Dermatol Res Pract. 2015;2015:260928. https://doi.org/10.1155/2015/260928
8. Pennisi RS. Acute generalised exanthematous pustulosis induced by the herbal remedy Ginkgo biloba. Med J Aust. 2006;184(11), 583–4. https://doi.org/10.5694/j.1326-5377.2006.tb00386.x
9. Zaraa I, Ben Taazayet S, Trojjet S, et al. Acute generalized exanthematous pustulosis induced by the essential oil of Pistacia lentiscus. Clin Exp Dermatol. 2012;37(4):361–3. https://doi.org/10.1111/j.1365-2230.2011.04232.x
10. Wu MY, Yen H, Wang CW, Chung WH. Curcumin-induced acute generalized exanthematous pustulosis. Indian J Dermatol Venereol Leprol. 2020;86:571–73. https://doi.org/10.4103/ijdvl.ijdvl_9_19
11. Ramirez-Santos A, Perez-Bustillo A, Gonzalez-Sixto B, Suárez-Amor O, Rodríguez-Prieto MA. Acute generalized exanthematous pustulosis due to milk thistle (Silybum marianum) tea. Actas Dermosifiliogr. 2011;102(9):744–5. https://doi.org/10.1016/j.ad.2010.12.019
12. Boccaletti V, Cortelazzi C, Fantini C, Tognetti E, Fabrizi G, Pagliarello C, Di Nuzzo S. Acute generalized exanthematous pustulosis following paracetamol ingestion in a child. Pediatr Allergy and Immunol. 2015;26(4):391. https://doi.org/10.1111/pai.12386
13. Chen YC, Fang LC, Wang JY. Paracetamol-induced acute generalized exanthematous pustulosis in a 4-year-old girl. Dermatol sin. 2016;1(34):49–51. https://doi.org/10.1016/j.dsi.2015.04.007
14. De Coninck AL, Van Strubarq AS, Pipeleers-Marichal MA, Huyghens LR, Suys ET, Roseeuw DI. Acute generalized exanthematous pustulosis induced by paracetamol: a case with severe hemodynamic disturbances. Dermatology. 1996;193(4):338–41. https://doi.org/10.1159/000246286
15. Campanón-Toro MV, Sierra O, Moreno E, Sobrino-García M, Gracia-Bara MT, Dávila I. Acute generalized exanthematous pustulosis (AGEP) induced by azithromycin. Contact Dermatitis. 2017; 76(6): 363–64. https://doi.org/10.1111/cod.12717.
16. Shah N, Rijal A, Mishra DR, Gallo ES. Triad of acute generalized exanthematous pustulosis, delirium, and lactic acidosis due to azithromycin. JAAD Case Rep. 2020; 6(12): 1254–57. https://doi.org/10.1016/j.jdcr.2020.09.026
17. da Cunha Filho RR, Bordignon SC, Cassol M, Rastelli GJ. Acute generalized exanthematous pustulosis by azithromycin. Int J Dermatol. 2015; 54(6): e247–9. https://doi.org/10.1111/ijd.12778.