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Drug Induced Acute Generalized Exanthematous Pustulosis: A Retrospective Case Series Analysis

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ABSTRACT

Acute generalised exanthematous pustulosis (AGEP) is a severe cutaneous adverse reaction, attributed to drugs in the majority (>90%) of cases, although it may also be associated with acute viral infections and mercury exposure. It is a rare condition, with an estimated incidence of 1–5 cases per million population per year. This study is a retrospective analysis of seven cases of drug-induced AGEP. Data were obtained from VigiFlow, a pharmacovigilance database used for adverse drug reaction reporting and analysis. Individual Case Safety Reports (ICSRs) of AGEP reported between July 2021 and February 2024 were analysed for patient characteristics, clinical presentation, outcomes, and suspected drugs. Causality and severity were assessed using the WHO-UMC causality scale and the Modified Hartwig and Siegel severity scale, respectively. Statistical analysis was performed using Jamovi version 2.3.28. Among the seven cases, there was a predominance of females (male:female ratio 1:6), with a mean age of 34.7 years. Antimicrobials were implicated in 85.7% of cases, while non-steroidal anti-inflammatory drugs (NSAIDs) accounted for 14.3%. Itching and fever were present in all cases, and leucocytosis was observed in 85.7% of patients. The mean latency period was 2.29 days. Based on severity assessment, 42.9% of cases were moderate and 57.1% were severe. According to the WHO-UMC causality scale, 57.1% of cases were classified as probable and 42.9% as possible. The mean resolution time was 8.71 days. AGEP is a rare but clinically significant adverse drug reaction; therefore, prompt recognition and reporting are essential. Strengthening pharmacovigilance systems is crucial for improving patient safety.

Keywords: Acute generalised exanthematous pustulosis, Cutaneous adverse drug reaction, Pharmacovigilance

INTRODUCTION

Acute generalized exanthematous pustulosis (AGEP) is a severe cutaneous adverse reaction, attributed to drugs in the majority (>90%) of cases; however, it may also be associated with acute viral infections and mercury exposure[1]. It is characterized by the rapid development of numerous non-follicular, sterile pustules on an erythematous base, most commonly involving the major flexural areas such as the neck, axilla, inframammary, and inguinal regions[1, 2].

The condition typically has an abrupt onset, usually occurring within 2–5 days of exposure to the suspected drug, and is associated with fever, pustulosis, and leukocytosis[2, 3]. Patients may also experience pruritus or a burning sensation over the affected areas[4]. Most cases are self-limiting and occur as a single episode; however, in severe cases, mucous membranes and systemic organ involvement may be observed[1].

AGEP is a rare disease, with an estimated incidence of 1–5 cases per million population per year[1, 2]. The majority of published reports on AGEP are single case reports. The most

commonly implicated drugs include Pristinamycin, Aminopenicillins, Quinolones, Chloroquine, Hydroxychloroquine, Sulphonamides, Terbinafine, and Diltiazem. Drugs with weaker associations include Macrolides, Non-steroidal anti-inflammatory drugs (NSAIDs), and Antiepileptic drugs[2].

MATERIALS AND METHODS

The study was conducted after obtaining approval from the Institutional Ethics Committee (PDUMCR/IEC/308/2024). This was a retrospective study. Data were collected from VigiFlow, a pharmacovigilance database used for the reporting and analysis of adverse drug reactions. The study period extended from July 2021 to February 2024.

Inclusion Criteria: All Individual Case Safety Reports (ICSRs) of drug-induced Acute Generalized Exanthematous Pustulosis (AGEP) reported to the Pharmacovigilance Programme of India (PvPI) at the Adverse Drug Reaction Monitoring Centre (AMC), Rajkot, during the study period (July 2021 to February 2024) were included.

All identified cases of AGEP were analysed for patient characteristics, clinical presentation, outcomes, and suspected drug(s). Causality and severity assessments were performed using the WHO-UMC causality scale and the Modified Hartwig and Siegel severity scale, respectively.

Statistical analysis was performed using Jamovi version 2.3.28.

RESULTS

A total of seven cases diagnosed with AGEP were reported. The epidemiological characteristics and clinical features of all cases are presented in Table. 1. Of the seven cases, six (85.7%) were female and one (14.3%) was male, with a female-to-male ratio of 6:1. The age ranged from 21 to 65 years, with a mean age of 34.7 ± 16.0 years. The latency period between exposure to the suspected drug and the onset of AGEP ranged from 0 to 5 days (mean 2.29 ± 1.60 days). None of the patients had a prior history of drug allergy or psoriasis.

In all cases, the lesions initially appeared on the face and neck and subsequently spread to involve the rest of the body. The palms and soles were affected in two cases (28.6%), while one case (14.3%) showed mucous membrane involvement (oral lesions).

All patients (100%) presented with itching and fever. Leukocytosis was observed in six patients (85.7%). Additionally, four patients (57.1%) had facial edema, and one patient (14.3%) presented with cervical lymphadenopathy. Regarding treatment, two patients (28.6%) received topical corticosteroids, while five patients (71.4%) were treated with systemic corticosteroids. All patients received supportive therapy, including antipyretics and/or antihistamines, as required.

With respect to etiology, six cases (85.7%) were attributed to antimicrobial agents, while one case (14.3%) was associated with a non-steroidal anti-inflammatory drug (NSAID), specifically Etoricoxib. Among the antimicrobial-related cases, two (33.3%) were associated with Amoxicillin. The remaining causative drugs (each accounting for one case, 16.7%) included Cefoperazone–Sulbactam (Cefosulbactum) with Chloroquine, Crystalline Penicillin, Vancomycin with Meropenem, and anti-tubercular therapy (Isoniazid).

The duration of lesions ranged from 6 to 14 days, with a mean resolution time of 8.71 ± 3.04 days. In all patients, resolution was accompanied by characteristic desquamation.

Of the seven cases, three (42.9%) were classified as non-serious, while four (57.1%) were serious and required intensive care. According to the Modified Hartwig and Siegel severity scale, three cases (42.9%) were moderate and four (57.1%) were severe. Based on WHO-UMC causality scale, four cases (57.1%) were probably and three cases (42.9%) were possibly related to the suspected drug(s). A summary of drug class in relation to severity and causality is presented in Table. 2.

Table 1: Epidemiological and Clinical characteristics of patients with AGEP

Parameter	Patient 1	Patient 2	Patient 3	Patient 4	Patient 5	Patient 6	Patient 7
Gender	Female	Female	Female	Female	Male	Female	Female
Age (years)	21	24	25	44	65	40	24
Latency period(days)	0	2	2	3	5	3	1
Suspected drug(s)	Cefosulbactum & Chloroquine	Amoxicillin	Amoxicillin + Clavulanate	Etoricoxib	Crystalline Penicillin	Vancomycin & Meropenem	Isoniazid
Itching	+	+	+	+	+	+	+
Fever	+	+	+	+	+	+	+
Palms/soles involvement	-/-	-/-	+/+	-/-	+/+	-/-	-/-

Parameter	Patient 1	Patient 2	Patient 3	Patient 4	Patient 5	Patient 6	Patient 7
Mucous membrane involvement	-	-	+	-	-	-	-
Facial edema	+	-	+	-	+	-	+
Lymphad-enopathy	-	-	-	-	-	-	+
Treatment	Topical Betametha-sone	Oral Prednisolo-ne	Intravenous Hydrocorti-sone	Oral Prednisolo-ne	Intravenous Hydrocorti-sone	Intravenous Hydrocorti-sone	Topical Betametha-sone

Table 2: Distribution of Drug Class in Relation to Severity and Causality

Drug Class	Number of Cases (%)	Severity		Causality	
		Moderate	Severe	Probable	Possible
Antimicrobials	6 (85.7%)	2	4	3	3
NSAIDs	1 (14.3%)	1	0	1	0
Total	7 (100%)	3	4	4	3

DISCUSSION

Acute generalized exanthematous pustulosis (AGEP) is currently recognized as a distinct clinical and histopathological entity with characteristic features, including the sudden onset of edematous erythema or scarlatiniform eruption that rapidly becomes covered with numerous small (<5 mm), predominantly non-follicular, superficial pustules (intraepidermal or subcorneal), accompanied by fever (>38°C) and peripheral leukocytosis[2, 5, 6]. The clinical manifestations, including pustules and fever, usually resolve spontaneously within two weeks, followed by characteristic desquamation[5, 7].

Less commonly, AGEP may be associated with localized lymphadenopathy, as observed in one of our patients, or with more severe manifestations such as generalized lymphadenopathy, pneumonia, or renal failure; however, these are typically acute and transient[5, 7]. Due to the presence of fever, leukocytosis, and widespread pustules, AGEP may be misdiagnosed as an acute bacterial infection. However, it is not caused by bacterial pathogens, and the pustular contents are sterile[1, 5].

In a minority of cases, AGEP may be triggered by viral infections, including Enterovirus, Adenovirus, Parvovirus B19, Epstein–Barr virus, Cytomegalovirus, Coxsackievirus, and Hepatitis B virus[2, 5]. It has also been associated with hypersensitivity reactions to mercury and spider bites[2]. Nevertheless, approximately 90% of reported cases are drug-induced. Commonly implicated drugs include Antimicrobials (particularly Aminopenicillins, Quinolones, Sulphonamides, and Macrolides), Antifungals (Terbinafine, Itraconazole, and Nystatin), Chloroquine and Hydroxychloroquine, Antiepileptic drugs, Allopurinol, Calcium channel blockers, and Paracetamol[1, 2].

To date, most published reports of AGEP are single case reports. The series of 63 cases reported by Roujeau *et al.*[7] has significantly contributed to the current understanding of AGEP. In comparison with the findings of Roujeau *et al.*, our series demonstrates several similarities and differences: (i) the mean age of patients was lower in our series (34.7 ± 16.0 vs. 49 ± 21 years); (ii) a female predominance was observed in both series; (iii) the latency period between drug exposure and onset of symptoms was shorter in our series (2.29 ± 1.60 vs. 5.1 ± 7.9 days); (iv) the occurrence of fever was comparable in both series (100% vs. 97%); (v) facial onset and facial edema were more frequent in our series (100% vs. 14% and 57.1% vs. 37%, respectively); and (vi) parameters such as lesion characteristics, mean time to resolution (8.71 vs. 10 days), and presence of leukocytosis (85.7% vs. 90%) were comparable between the two series.

Regarding pathogenesis, AGEP is considered an immune-mediated reaction in which drug-specific T cells play a central role by producing large amounts of neutrophil-attracting cytokines, particularly interleukin-8. This results in neutrophil accumulation at the site of lesions, a hallmark feature of AGEP. It has been suggested that CD4+ T cells, and possibly CD8+ T cells, act as early responders and contribute to vesicle formation. Subsequently, polymorphonuclear cells migrate into the lesions, fill the vesicles, and transform them into pustules. Additional immune mechanisms may also contribute to the variability in clinical presentation. For instance, increased interleukin-5 production by T cells in both tissue and serum, along with enhanced eotaxin production, may explain the eosinophilia observed in some cases. Furthermore, keratinocytes play an important role by expressing cytokines that attract neutrophils and eosinophils to the affected sites[2, 5-7].

CONCLUSION

Drug-induced AGEP typically occurs within five days of exposure to the causative drug, with antimicrobials being the most commonly implicated agents. The condition primarily involves the skin; however, mucous membrane involvement may occur in a minority of cases. The characteristic clinical features include itching, fever, and leukocytosis. Management often requires topical or systemic corticosteroids. AGEP generally resolves within two weeks, followed by characteristic desquamation.

The estimated incidence of AGEP is 1–5 cases per million population per year. However, it may be underreported due to frequent misdiagnosis as pustular psoriasis or infectious conditions presenting with fever, leukocytosis, and pustules. Increased awareness and familiarity with the clinical features of AGEP among clinicians can facilitate accurate diagnosis and appropriate management. Given its rarity, reporting of such adverse drug reactions is essential. Strengthening pharmacovigilance systems remains crucial for improving patient safety.

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