SHORT COMMUNICATION

Ampicillin-induced Acute Generalized Exanthematous Pustulosis in a Neonate: A Rare Cutaneous Adverse Reaction

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Acute generalized exanthematous pustulosis (AGEP) is a rare, acute, severe cutaneous adverse reaction primarily caused by drugs. It is characterized by the acute onset of erythema, predominantly in the major skin folds with multiple pinpoint non-follicular sterile pustules (1). AGEP is more frequently observed in adults, and is rarely reported in children, particularly in newborns (2, 3). To the best of our knowledge, there have been no reports of drug-induced AGEP in neonates. Ampicillin and cefotaxime constitute a common empirical antibiotic regimen in neonates. Here, we report a case of ampicillin-induced AGEP in a neonate.

CASE REPORT

A male neonate, at 2 h old, was emergently transferred to our neonatal intensive care unit (NICU) with severe respiratory distress caused by meconium aspiration syndrome, necessitating immediate endotracheal intubation and positive pressure ventilation. Administration of fentanyl citrate injection at 1 μg/kg/h via intravenous infusion provided analgesic sedation. On the afternoon of admission, empirical antibiotic therapy was commenced with ampicillin sodium (150 mg/kg/day) combined with cefotaxime sodium (100 mg/kg/day) administered intravenously. A penicillin skin test performed prior to antibiotic administration yielded a negative result.

On the second day of empiric antimicrobial therapy, acute onset of erythema was first observed by a paediatrician, predominantly on the face, abdomen, and limbs. Within 24 h, the rash progressed into generalized pustular eruption, characterized by a large number of needle-tip-sized pustules all over the body; some of the pustules were fused (**Fig. 1**). There was no fever. Laboratory investigations revealed significant leukocytosis with neutrophilia, marked by a white blood cell (WBC) count of 43.98 × 10^9/L and an absolute neutrophil count (ANC) of 31.71 × 10^9/L, with a neutrophil proportion of 72.10%. Microscopic examination further revealed a left shift in neutrophils. Notably, C-reactive protein (CRP) levels were within normal limits at 3.00 mg/L. Liver function testing showed elevated total bilirubin (TBIL) at 85.5 μmol/L, likely attributable to physiological jaundice in the neonatal period. Following dermatological consultation, AGEP was suspected by the dermatologist based on the characteristic clinical presentation. Bacterial cultures of pustular lesions and serial blood cultures were negative. A skin biopsy was not performed due to the patient's young age and parental refusal of the procedure.

The pharmacovigilance team, according to the Euro Severe Cutaneous Adverse Reactions (EuroSCAR) criteria, assigned an AGEP diagnostic score of 8 (**Table I**) (4). Given the temporal association with antimicrobial therapy, a hypersensitivity reaction to ampicillin was strongly suspected. Ampicillin was immediately discontinued, while cefotaxime was continued for concurrent infection management, and the patient was treated with topical corticosteroids and emollients. Following discontinuation of ampicillin, the pustules rapidly subsided. In particular, the pustules ceased spreading within 24 h and began to dry, forming scales after 2 days. However, a few scattered small, red papules and macules remained on the body. After 6 days, all red papules resolved but with marked post-purulent desquamation (**Fig. 2**). Concurrently, the patient was successfully weaned off the ventilator. The patient recovered completely and was discharged at 14 days.

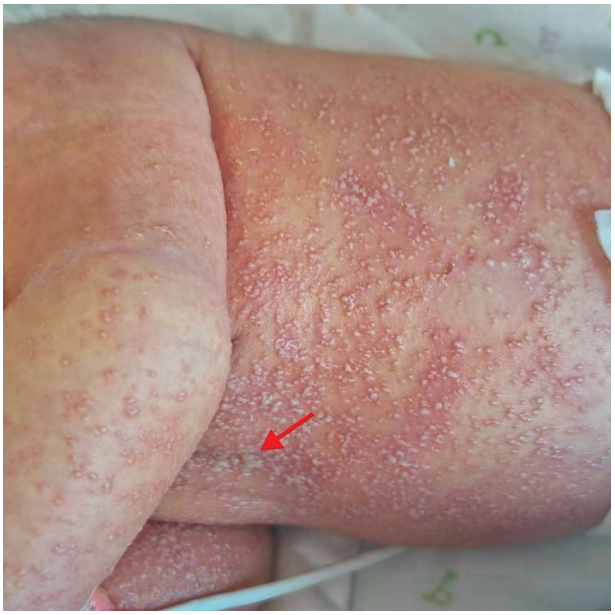

Fig 1. Multiple sterile, needle-tip-sized pustules on a background of widespread erythema (arrow indicates the fusion of pustules).

DISCUSSION

AGEP is an uncommon, severe type IV hypersensitivity drug reaction, with the majority of cases thought to be caused by medication. The main causative drugs are

Table I. AGEP validation score of the Euro-SCAR

Category	Description	Score
Morphology		
Pustules	Typical, multiple pinpoint non-follicular sterile pustules	+ 2
Erythema	Typical, acute onset of erythema	+ 2
Distribution/pattern	Typical, on the face, abdomen, and limbs	+ 2
Post-pustular desquamation	Yes	+ 1
Course		
Mucosal involvement	No	0
Acute onset (≤ 10 days)	Yes	0
Resolution (≤ 15 days)	Yes	0
Fever ≥ 38°C	No	0
Neutrophils ≥ 7,000/mm³	Yes	+ 1
Histology	Not representative/no histology	0
Total score		8

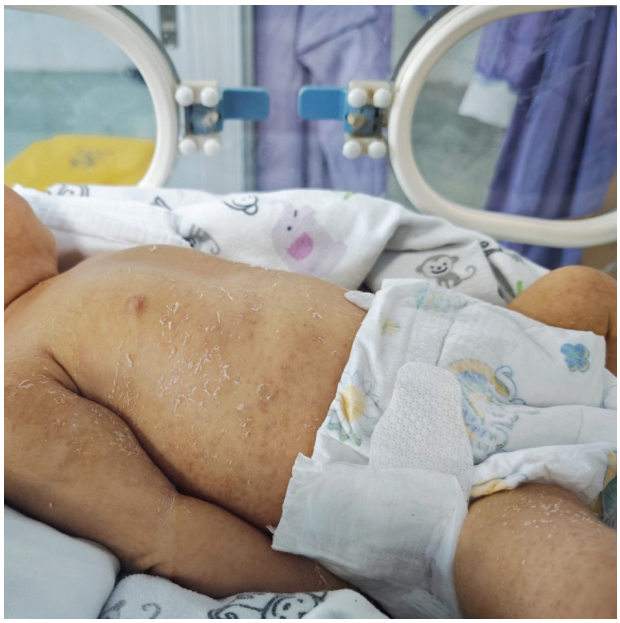

Fig 2. The red papules resolved but with marked post-purulent desquamation.

antibacterials for systemic use, including penicillins, cephalosporins, macrolides, quinolones, and others. Other frequently reported suspected drugs are antineoplastic agents, anti-inflammatory and anti-rheumatic drugs, and hydroxychloroquine (4). AGEP typically presents as an acute pustular eruption accompanied by leukocytosis within 24–48 h of exposure to the offending drug (5). Antibiotic-induced cases are characterized by a particularly rapid onset, with a median time of 24 h. In contrast, AGEP triggered by other drugs may present with a longer latency period, ranging from 10 to 22 days (1). Prodromal signs include fever and generalised malaise with leukocytosis, particularly neutrophilia, with eosinophilia in up to 30% of patients (5). In this patient, there was an acute onset within 24 h of initiating systemic antimicrobials, and laboratory tests showed markedly elevated leukocytes and neutrophils, with normal eosinophil levels and no fever.

The diagnosis of AGEP in children, particularly neonates, remains challenging, as most epidemiological and clinical data are derived from adult cohorts, and key assessment tools such as EuroSCAR have only been validated in adults. However, the clinical presentation and histopathological features of AGEP in children are similar to those observed in adults (6). Although dedicated studies are lacking, it is widely acknowledged by authoritative bodies that the incidence of AGEP in children is significantly lower than in adults. In this population, the most common offending drugs appear to be anti-infectious agents, especially aminopenicillins (7, 8). Notably, infection may play a more prominent role in the pathogenesis of AGEP in paediatric patients compared with adults (9). In newborns, a case of AGEP due to Epstein–Barr virus (EBV) infection has been reported (10). To the best of our knowledge, this is the first reported case of AGEP associated with ampicillin in a neonate.

In neonates, several benign pustular dermatoses may clinically mimic AGEP and should be considered. Transient neonatal pustular melanosis (TNPM) typically presents at birth with 1–3 mm flaccid, superficial pustules lacking surrounding erythema; the lesions rupture within a few days and leave characteristic pigmented macules that may persist for weeks to months (11). In contrast, AGEP usually appears after drug exposure, is accompanied by diffuse erythema, fever, and neutrophilia, and resolves rapidly after withdrawal of the offending agent. Another important differential is miliaria pustulosa, which arises from sweat duct obstruction and manifests as superficial pruritic pustules over areas such as the upper back, forehead, and flexures, often in a warm or humid environment (12). Unlike AGEP, miliaria pustulosa is not drug-induced, is self-limiting, and lacks systemic symptoms. Recognition of these characteristic clinical and chronological distinctions is critical to avoid misdiagnosis and unnecessary interventions in newborns.

There is no definitive treatment for AGEP. It is important to recognize it clinically and histologically and to remove any potential offending medications. In this case, a pustular rash developed within 48 h of initiating systemic antibiotic therapy, leading the dermatologist to suspect AGEP based on its characteristic presentation. The clinical pharmacy service team promptly conducted a review of the drug prescribing information and relevant literature. Integrating the infant's medication timeline and considering the persistent high risk of infection, we recommended discontinuation of ampicillin and maintaining cefotaxime therapy, accompanied by intensive monitoring for the resolution of the adverse drug reaction.

Our case expands the limited knowledge of drug-induced AGEP in neonates. Awareness of the potential for serious cutaneous adverse drug reactions is essential, but such recognition should not deter the judicious use of antibiotics when clinically justified. Instead, it should foster heightened vigilance, systematic pharmacovigilance reporting, and timely intervention, ensuring that therapeutic decisions optimize both efficacy and safety in neonatal care.

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