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Case Report

# Ceftriaxone induced acute generalized exanthematous pustulosis confirmed with patch test

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## ABSTRACT

**Background:** Acute generalized exanthematous pustulosis (AGEP) is a rare cutaneous drug reaction presenting with rapid-onset sterile pustules on edematous erythema.

**Case:** A 12-year-old female patient with acute gastroenteritis was consulted with complaints of pruritic erythema and high fever developing with small pustules on the 2nd day of ceftriaxone treatment. Lab tests showed an elevated absolute neutrophil count and lymphopenia. Ceftriaxone was discontinued immediately. The fever went away within 24 hours. According to EuroSCAR, the diagnosis of AGEP was confirmed. The skin biopsy was compatible with AGEP. After 6 weeks, a patch test with ceftriaxone was performed. A strong positive reaction to ceftriaxone was detected. Three months later, amoxicillin, amoxicillin-clavulanate, clarithromycin, and trimethoprim/sulfamethoxazole patch tests were performed, all were negative, and provocation tests were also planned.

**Conclusion:** AGEP is a severe cutaneous drug reaction. We wanted to emphasize that patch tests help identify the responsible drug and find a safe alternative.

**Keywords:** Acute generalized exanthematous pustulosis, drug eruption, patch test, severe drug hypersensitivity reactions

## INTRODUCTION

Acute generalized exanthematous pustulosis (AGEP) is a rapid-onset cutaneous drug reaction that presents as non-follicular sterile disseminated pustules on an edematous erythematous background. Peripheral blood leukocytosis and fever are frequently seen in patients.[1] Usually drugs, especially antibiotics, cause AGEP and there have been rare cases of viral infections (e.g. enterovirus) and exposure to inorganic compounds (e.g. mercury) or contrast agents.[1-3] Patch testing, a safe and useful in vivo test, is used to find the causative agent.[2] In this report, we present a patient with ceftriaxone-induced AGEP, which was confirmed by patch testing and skin biopsy.

## CASE

A 12-year-old girl was admitted to a secondary health care institution due to complaints of vomiting and diarrhea that started one week ago, and fever three days ago. She was diagnosed with acute gastroenteritis and started on parenteral

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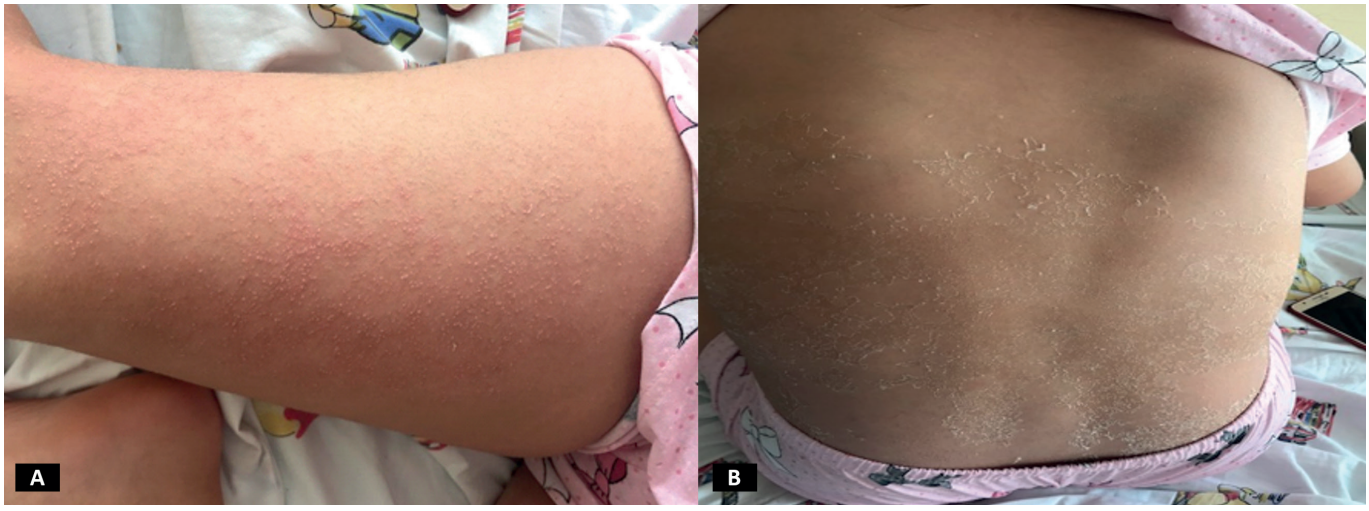


**Figure 1.** (A) Erythaema with numerous small non-follicular pustules. (B) Desquamation of lesions on the back.

hydration and ceftriaxone. The next day, she was referred to our hospital with prerenal renal failure due to increased urea, creatinine, and uric acid levels. Because of the COVID-19 pandemic, the patient was hospitalized after obtaining a COVID-PCR test, and continued hydration and ceftriaxone treatment. At 48-72 hours of ceftriaxone treatment, she developed pruritic erythema growing with multiple small non-follicular pustules associated with fever (39°C), most commonly in the inguinal and axillary regions, as well as on the trunk, face, and proximal limbs (Figure 1A). The patient's gastrointestinal, respiratory, and lymph node examinations of the patient did not reveal any features, and there was no mucosal involvement. Her personal and family history was unremarkable. Laboratory tests showed leukocytosis (21100/mm$^3$, absolute neutrophil count: 19200/mm$^3$) and lymphopenia (800/mm$^3$ [%6,9]). Urea, creatinine, and uric acid levels improved. An infectious etiology was excluded through PCR test, antibody response (for COVID-19), viral serology (for CMV, EBV VCA, Parvovirus B19, HSV tip1 IgM), and blood and throat swab cultures were all negative. Ceftriaxone was thought to be the culprit drug and was discontinued, and the patient's fever regressed within 24 hours. Desquamation (Figure 1B) started on the 3rd day after ceftriaxone was discontinued, and the skin was completely healed on the 10$^{th}$ day. According to the AGEP scoring system of the EuroSCAR study group, which we performed according to the history, clinical, and laboratory findings, our patient got 11 points (Table 1) and the diagnosis of AGEP was confirmed. We performed a skin biopsy which showed subcorneal, intraepidermal non-follicular pustules containing neutrophils, consistent with AGEP (Figure 2A). The immunohistochemical study revealed accumulations stained with IL 17 (Figure 2B).

**Table 1. The patient's EuroSCAR scoring (AGEP validation score)**

| | | |
|---|---|---|
| **Morphology** | Typical Pustules | 2 |
| | Typical Erythema | 2 |
| | Distribution pattern Compatible | 2 |
| **Course** | Mucous membrane involvement (No) | 0 |
| | Acute beginning (Yes) | 0 |
| | Resolution within 15 day (Yes) | 0 |
| | Fewer >38 0C (Yes) | 1 |
| | Polymorphonucleer cells >7000 /mm3 (Yes) | 1 |
| **Histology** | Involves subcorneal, and/or intraepidermal pustules with papillary edema | 3 |
| **Total score** | | 11 |

Six weeks after the reaction, a patch test with ceftriaxone was performed. A drop of ceftriaxone (200 mg/ml) and a drop of normal saline (as negative control) were applied to the skin on the child's upper back using IQ Chambers on 9 mm adhesive tape. The occlusion time was 48 h; 15 min after the removal of the cups and readings were recorded on day two and day four, according to the current guideline.[2] A strong positive reaction (++) to ceftriaxone was documented with infiltrated erythema and pustules (Figure 3).

To determine the safe alternative antibiotic, we performed further patch tests three months after her discharge with beta-lactams such as amoxicillin and amoxicillin-clavulanate (which do not share the same side chain with ceftriaxone) and non-beta lactam antibiotics that are clarithromycin and trimethoprim-sulfamethoxazole. Amoxicillin and amoxicillin-clavulanate

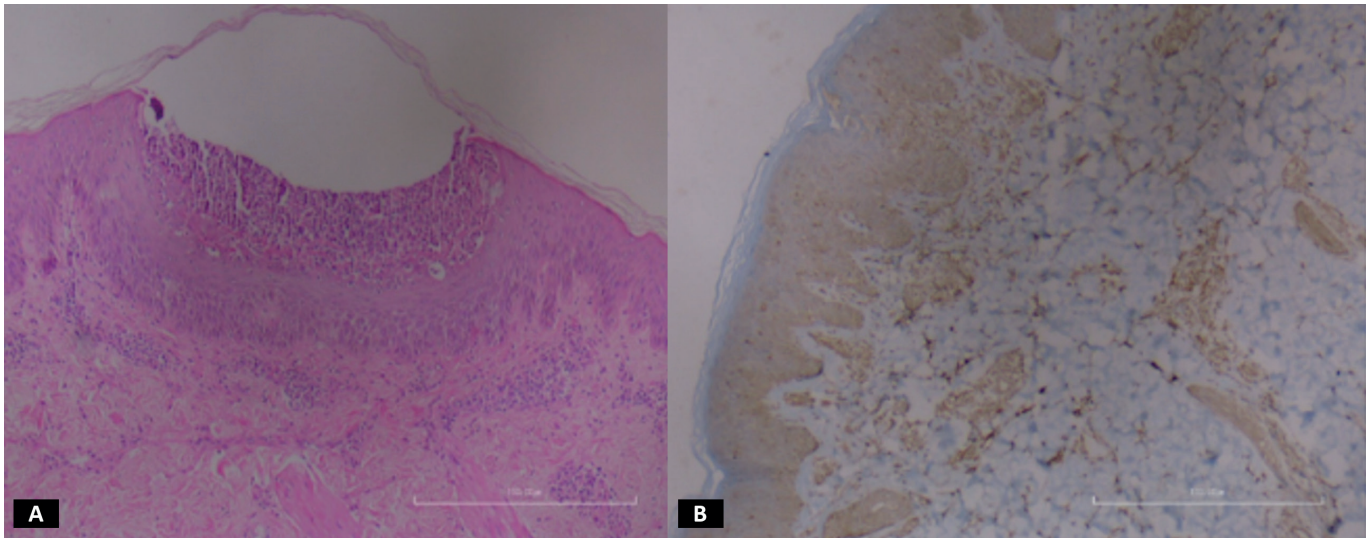


**Figure 2.** (A) Subcorneal pustule, epidermal spongiosis, neutrophil exocytosis, superficial perivascular mixed inflamation including rare eosinophils. Hematoxylen and eosine x100. (B) Deposits stained with IL-17 in the dermis.

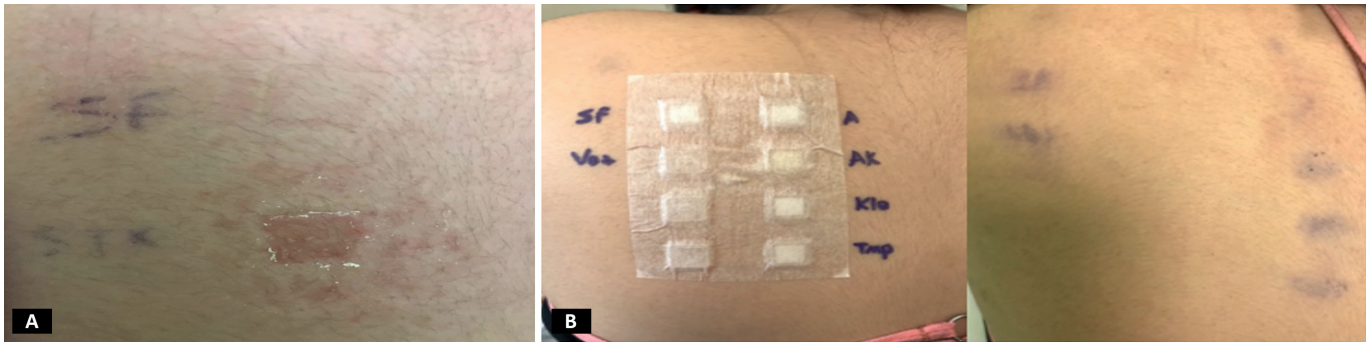


**Figure 3.** (A) A strong patch test reaction with ceftriaxone on day 2. (B) Negative patch tests with moxicilin, amoxicilin-clavulanate, trimethoprim/sulfamethoxazole, clarithromycin.

tablets were diluted 30% in petrolatum, drops of trimethoprim/sulfamethoxazole (80 mg/ml), and clarithromycin (50 mg/ml). Normal saline and petrolatum were used as negative controls. They were all negative at 48 and 72 hours (Figure 3).

## DISCUSSION

AGEP is a rare adverse drug reaction with a frequency of one to five cases per million per year and is a severe pustular reaction characterized by acute onset, non-follicular pustules with high fever and leukocytosis.[1] Mild oral mucosal involvement may occur in about 20 percent of cases with AGEP. Pustules resolve within a few days (average 4-10), followed by post-pustular punctate peeling patches.[4] In a retrospective study of 63 AGEP cases, Roujeau et al.[5] characterized this incidence as drug-induced. Beylot et al.[6] reported that drugs were involved in 90% of cases and antibacterials were the most common triggers. The β-lactam antibiotic group is responsible for the majority of antibiotic-associated AGEP cases[6] as was the case with ceftriaxone in our patient. The period between the start of the drug and the onset of AGEP symptoms varies; 24-48 hours for common causative agents such as penicillin and 10-14 days for other high-risk drugs.[1] The periods between the administration and cessation of ceftriaxone and the onset of symptoms were 2 and 10 days respectively, as reported in the literature.[4]

Generalized pustular psoriasis (GPP), follicular pustular diseases, Drug reaction with eosinophilia and systemic symptoms syndrome (DRESS), Steven-Johnson syndrome (SJS), and toxic epidermal necrolysis (TEN) should be considered in the differential diagnosis of AGEP. It has been suggested that a mutation in the IL-36RN gene results in a decrease or inefficacy

of the IL-36 receptor antagonist (IL-36Ra) and an uncontrolled increase in IL-36. Increased IL-36 signaling causes IL-1α, IL-1β, IL-6, and IL-8 production and may predispose to pustular formations.[7] Recent studies have identified similarities in the pathogenesis of AGEP and GPP, such as mutations detected in IL-36Ra and increased expression of IL-17 by TH17 cells.[8,9] However, the distinction between the two diseases is based on several specific features. Only a minority of AGEP patients has a history of psoriasis and AGEP has a much shorter course than psoriasis.[1]

AGEP differs from follicular pustular diseases because it is an example of non-follicular pustulosis. Two other follicular pustular diseases to consider in the differential diagnosis are subcorneal IgA dermatoses and Sneddon-Wilkinson disease (subcorneal pustulosis). These two diseases differ from AGEP by the presence of large pustules that occur subacutely.[10]

In distinguishing AGEP from severe cutaneous drug reactions, Dress syndrome has a long latent period, typically 2 to 6 weeks, and an erythematous morbilliform rash is typical. Mucosal and visceral involvement is more common than in AGEP.[11] SJS and TEN are characterized by Nikolsky signs and mucosal involvement. Therefore, it may be difficult to distinguish SJS/TEN from severe AGEP cases with mucous membrane involvement. However, TEN also presents with full-thickness epidermal necrosis and a lymphocytic infiltrate at the dermo-epidermal junction.[12]

Determining the cause of cutaneous adverse drug reactions (CADR), skin tests are helpful in identifying the cause of CADR.[13] Because the patch test shows positive results, AGEP is recognized as a delayed type of hypersensitivity reaction, which is one of the CADRs.[14]

Diagnostic approaches for delayed hypersensitivity reactions include patch testing, delayed intradermal testing (IDT), and drug provocation tests for milder reactions. Unfortunately, guidelines for performing IDTs have not been standardized and have unknown values.[15] Provocation tests should not be performed in severe cutaneous drug reactions such as AGEP.[16] Since re-exposure to the drug may lead to another episode of AGEP, causality assessment after the acute phase is over is a very important procedure.[17] Positive patch test results are more common in AGEP than those in SJS/TEN, usually showing many small sterile pustules at the test site.[14] Patch testing has been reported to be a safe diagnostic method and found to be positive in 58 % of patients with AGEP[2] and we performed it without any problems in our patient.

Patch tests can also help examine the ability of drugs to elicit symptoms due to cross-reactivity, e.g. among beta-lactam antibiotics.[18] Patients with a positive patch test result for cephalosporin should not be tested with another molecule that shares the same side chain due to the higher risk of cross-reactivity.[19] To find a safe alternative antibiotic, we applied a patch test with antibiotics with different side chains that are frequently prescribed by physicians. When choosing medications that can be used safely, a patch test can be done beforehand, and if it is negative, a provocation test is appropriate. Our patient had a history of using amoxicillin-clavulanate and clarithromycin safely. However, we still planned to perform a provocation test with drugs that were positive in the patch test.

## CONCLUSION

We emphasize that AGEP should be kept in mind by clinicians since it is a very rare disease. In addition to the frequent occurrence of ceftriaxone as the culprit in the literature, the number of cases confirmed by patch testing in childhood is very low. We also want to emphasize that patch tests are useful not only for defining the culprit drugs in AGEP but also for finding safe alternatives.

### Author contribution

Surgical and Medical Practices: ÖTU; Concept: PGÖ; Design: ÖTU; Data Collection or Processing: SKS; Analysis or Interpretation: ÖTU, PGÖ; Literature Search: ÖTU, MY; Writing: ÖTU, NC. All authors reviewed the results and approved the final version of the article.

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### Conflict of interest

The authors declare that there is no conflict of interest.

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