Title: Acute Generalized Exanthematous Pustulosis Due to Cephalexin: A Case Report and Literature Review

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Abstract

Introduction: Acute generalized exanthematous pustulosis (AGEP) is a cutaneous reaction that can be appeared after the use of certain medications, such as cephalexin, with non-follicular sterile pustules, erythematous, urticaria, fever over 38℃ and leukocytosis. Cephalexin belongs to the family of beta-lactam antibiotics, which are widely used around the world to treat infections. However, cephalexin skin sensitivities have been reported worldwide once in a while. Herein, in this case, we aimed to report a patient presented with AGEP due to cephalexin usage.

Case report: A 12-year-old boy presented with warmth, skin lesions that gradually appeared on the other limbs, trunk, face, and neck after taking cephalexin powder arbitrarily on his left leg. Due to his symptoms, acetaminophen, fexofenadine hydrochloride, loxoprofen sodium and ointment including difluprednate and hydrocortisone were prescribed. Over time, the patient's fever subsided, and 8 days later, the symptoms of AGEP, including urticaria, erythematous, and pustules in the neck and trunk disappeared.

Conclusion: Cephalexin is one of the antibiotics that is considered by doctors and patients when there is a possibility of infection. AGEP is a rare but severe reaction that can develop into skin rashes of any age and sex following the use of cephalexin, paying attention to this issue forces the patient to be careful when using this antibiotic.

Keywords: Acute generalized exanthematous pustulosis, Cephalexin, Adverse drug reaction

Introduction

Acute Generalized Exanthematous Pustulosis (AGEP) is a rare cutaneous adverse reaction, which occurs after using some drugs or infection. It is characterized by the sudden appearance of many non-follicular sterile pustules on an erythematous background (1). Belott, et al. first introduced this type of skin rashes in 1980 in France. The patients did not have psoriasis; their symptoms improved spontaneously after an attack and were obtained by histological examination of dermal vasculitis in addition to nonfollicular Sub-corneal Pustules (2). It is anticipated that AGEP occurs one to five cases per million people per year (3). Although, AGEP often affects middle-aged adults but occurring at any age might be possible. Both sexes (with an insignificant prevalence in women) would be affected. The AGEP mortality rate is about 5% (1).

AGEP symptoms including pimples, which appeared on the face or areas of the skin folds and spreads within 24 hours, although late symptoms have been mentioned up to 3 weeks after taking the drug. The ebullition of pustular have been seen after postpustular desquamation. Serious cases of AGEP may appear with unusual lesions and conjunct pussy pimples, leading to extensive surface erosion and redness on the skin, which potentially similar to SJS /TEN. In AGEP, the mucous membranes are not affected and usually erosion of the lips is seen (1). Skin rashes are uncommon for more than 2 weeks; fever (>38°C) and leukocytosis (neutrophil / ml 7000<) are usually presented with mild eosinophilia. Visceral involvement is rare (4).

AGEP is being developed following insects bite, sensitivity to contact (5) and using several drugs, including anti-malarial drugs (hydroxychloroquine), calcium channel blockers (diltiazem) (1), amoxicillin, clavulanic acid, pristinamycin, ampicillin, co-trimoxazole, terbinafine, carbamazepine , spiramycin , metronidazole (6) and in rare cases , cephalexin (7). Cephalexin is taken by mouth as a capsule, tablet, and suspension (liquid) (8), skin (9), and parenteral (10). Some studies have shown that parenteral use of cephalexin has more side effects than oral use, but this has not yet been proven (10, 11). There are few reports about AGEP as one of the uncommon side effects of cephalexin. According to these reports, the patient started taking cephalexin and after a few days, the symptoms of AGEP appeared as erythema and pustules in different parts of the body. By stop using cephalexin, the symptoms have been improved (7, 12). In this case, we aimed that report a 12-year-old boy who presented to the pediatric clinic with the symptoms of AGEP after

using cephalexin. We hoped that previous reports and ours, help physicians considering AGEP as an adverse reaction in their differential diagnosis.

Case presentation

A 12-year-old boy was referred to the pediatric clinic with a complaint of 10-day history of skin lesions and itching throughout the body (Fig.1) and having mild fever for the past 2-3 days. He stated a history of injury to his left leg with a sickle while working on a farm from 20 days ago.

The patient arbitrarily used cephalexin capsule powder 500 mg on the wound for 48 hours, 3 times a day. About 10 days later, when itching and urticaria lesions appeared at the site of the wound, hydroxyzine syrup 5cc arbitrarily used two times a day for the last 48 hours. Erythematous and urticaria lesions progressively spread to other limbs, trunk, face, and neck. At the same time, pustular lesions formed on the neck and trunk, on urticaria lesions. The history of hospitalization, specific illness, urticaria, and eczema were denied. There is a suspicion of cephalexin side effects.

On physical examination, the patient was conscious, not toxic and ill. His body temperature was 38.1 ℃(axillary), but other vital signs were normal. Urticaria lesions were seen all over the body. Sub epidermal and intraepidermal postural lesions accompanied by itching were seen especially on the urticaria and erythematous areas of the neck and trunk. A 5 cm long crusted wound was also seen on the left leg (Fig.2). Other examinations were normal.

In the laboratory, tests did not show any abnormalities except for leukocytosis (13000 mm3/L) and also serologic tests for infections and viruses like Cytomegalovirus, Epstein–Barr virus, Human Herpesvirus-6, and Hepatitis B and C viruses were negative.

Acetaminophen 2,400 mg/day, Fexofenadine hydrochloride 120 mg/day, Loxoprofen sodium 60 mg/day, and an ointment including Difluprednate and Hydrocortisone were prescribed. After a while, the fever has subsided. Approximately 8 days after, urticaria and pustular lesions were improved. After two weeks, all the laboratory tests were normal.

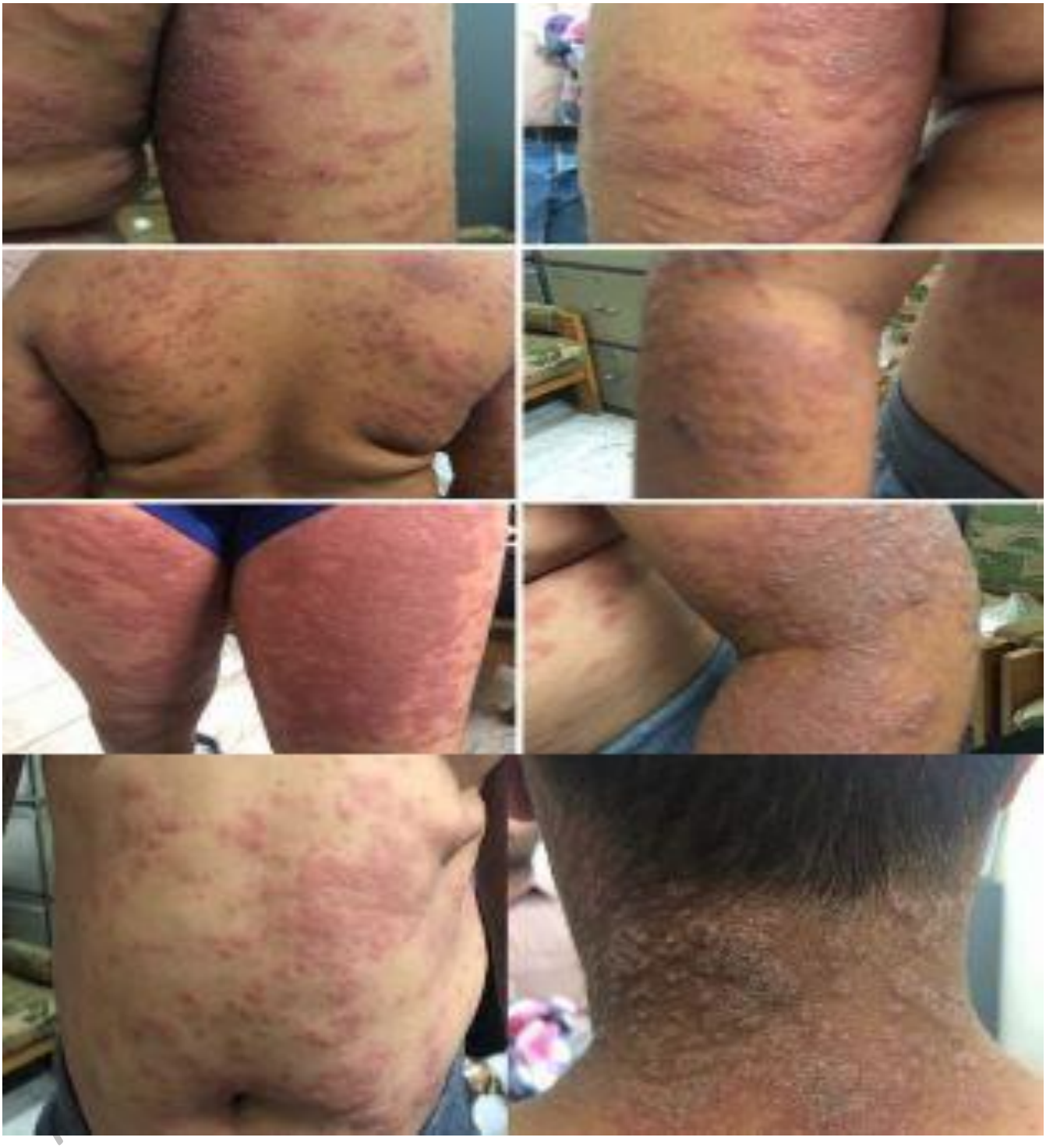

Fig. 1. Sub epidermal and intraepidermal postural lesions

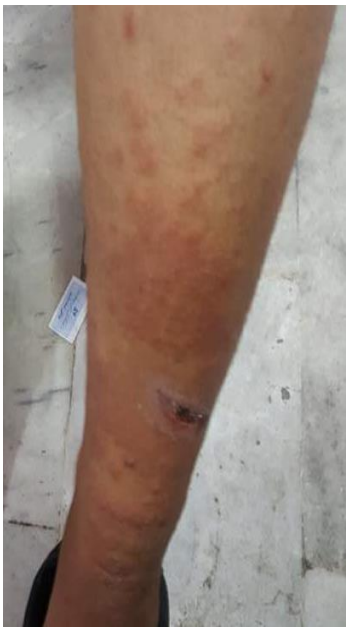

Fig.2. Crusted wound on the left leg

Discussion

AGEP is a self-limiting reaction (13), and the role of genetics in its development and appearance is unclear (14). It's a subtype of a type IV reaction with a role for both CD4+ and CD8+ T cells (14). Clinical and histological criteria are needed for Diagnosing AGEP (3). Histological tests are the first test used to differentiate AGEP, for this reason, a skin biopsy is used. Typically, biopsy results show papillary edema, neutrophilic spongiosis and subcorneal pustules, and perivascular infiltrate with neutrophils and some eosinophils. In some cases, necrotic keratinocytes and leukocytoclastic vasculitis have been reported (14). Skin biopsy could be used to confirm the diagnosis and also reject other causes of pustular eruptions (1). Histologically, it is very difficult to diagnose AGEP disease from generalized pustular psoriasis (GPP), but the presence of eosinophils, necrotic keratinocytes, and vascular excretion in the absence of fragile blood vessels is good evidence for AGEP diagnosis. While in GPP, the presence of psoriasiform acanthosis is a diagnostic factor (14). It is vital to pay attention to recent prescriptions, clinical course, and histopathological characteristics, which conduct to distinguish between AGEP and generalized pustular psoriasis (4). Another way to diagnose AGEP is through patch tests. The important thing about this test is that the patch test is more sensitive to AGEP than similar reactions such as TEN

and SJS. Positive test results are identified as small pustules at the test site (13). The validation score of AGEP (EuroSCAR group Criteria) is a practical tool for diagnosing (5). This validation score consist of the morphology of skin lesions, the presence of fever, the clinical course, and the laboratory and histopathological findings (3).

Although there is no particular treatment for AGEP but discontinuation of annoying medications, topical corticosteroids, and antipyretics could be useful (14). Symptoms usually go away in a few days, but older people or patient with immunodeficiency with a widespread manifestation of skin rash may still need to be hospitalized to receive fluid and electrolyte support (3).

Cephalexin is the first generation of cephalosporin antibiotics from beta-lactam family (15), which is widely used for treating infections in the respiratory system, soft tissue, and genitals (16). Cephalosporins usually have the highest percentage of prescriptions due to their widespread clinical use and also are well tolerated among antibiotics. About 1-3% of people have a history of allergies to cephalosporins. Cephalosporins side effects include about 1 to 5% of skin signs, such as maculopapular or morbilliform, ebullition of skin rashes, urticaria, and also eosinophilia, Fever, anaphylaxis, angioedema, rhinitis, and bronchospasm. These symptoms approximately can appear 1 hour after taking the drug (15). Dyspepsia, gastritis, diarrhea, abdominal pain, and urticarial are side effects of cephalexin and AGEP is one of the rarest side effect (7). Cephalexin makes skin lesions such as violaceous macular rash, erythematous, and numerous big skin lesions on the neck and abdomen (17).

Based on Matthew DaCunha et al. (7) and our knowledge, there have been four reports of AGEP related to cephalexin. Our case will probably be the 5th case of cephalexin induced AGEP. Describing and comparing previous reports can help further knowledge in the diagnosis of AGEP due to cephalexin and provide statistical review and conclusions. Studies have shown that previous cases are adults who have taken cephalexin capsules with a doctor's prescription. While our case is the first 12-year-old adolescent patient to use cephalexin powder arbitrarily on his left foot ulcer. Of the 4 cases reported, three were female (7, 18, 19) and one were male (12) such as our case, indicating more females involvement. In the 2 previous patients (12, 18) and also in our patient, the history of any skin disorders has been rejected, and only in one case (19) a history of skin disorders was reported. The time of starting symptoms varies after taking cephalexin. These times are including two days after the first use of cephalexin (19) up to 4 days after the last use (12), in

our patient this time is about 10 days after the first use. In most of the previous cases and the case we studied, the appearance of erythematous, itching, urticaria lesions, fever, and skin eruptions in different areas of the skin of the body and limbs are common. In one case, the skin eruptions were limited to the left hand (7). One of the most surprising symptoms is nausea and vomiting in only one case (12). So far, no visceral conflicts have been reported following cephalexin use, which could be a positive point. In most of the cases studied, as in our case, the bacterial culture result was negative (7, 18, 19) and the CBC result show leukocytosis (19). The first treatment that has been considered in all cases is the discontinuation of cephalexin. The second step is corticosteroid supportive therapy, which is not necessary but helps the healing process. In one case, acitretin and cyclosporine were prescribed, and the recovery time was about one to two weeks after starting treatment (19). Supportive therapies for us included acetaminophen, fexofenadine hydrochloride, loxoprofen sodium, and an ointment including Difluprednate and hydrocortisone, which improved the patient within days. One of the limitations of this case was the lack of biopsy to diagnose AGEP, although this complication is self-limiting and its diagnosis is based on clinical signs. It should also be noted that skin biopsies are mostly used in studies that have a research aspect. Due to the lack of accurate determination of the mechanism of occurrence of this complication, it is necessary to review articles on this issue analytically.

Conclusion

Cephalexin is one of the antibiotics that is considered by doctors and patients when there is a possibility of infection. AGEP is a rare but severe reaction that can develop into skin rashes of any age and sex following the use of cephalexin, paying attention to this issue forces the patient to be careful when using this antibiotic. One of the best ways to diagnose AGEP, in addition to the symptoms, is the biopsy and laboratory tests. Proper diagnosis of AGEP and discontinuation of cephalexin is the first effective step in treating the affected patient. It is not necessary to take steroids because AGEP is self-limiting but can be effective in increasing the speed of improving symptoms.

Table 1. Description of five cases of cephalexin-induced AGEP

Authors	Age/Sex	Cephalexin dosage	Cause of consumption	time of occurring symptoms	The first place starting symptoms	Symptoms	Recovery time
Arroyo, M. P. (18) (2002)	47/F	Not reported	Not reported	Not reported	Not reported	diffuse pustules and edema of the skin	Not reported
Holscher, C. M. (12) (2011)	58/M	Not reported	hair transplant	4 days after stopping the drug	erythema in his groin, neck, and axilla	nausea, vomiting, diarrhea, erythema in groin, neck, and axillae, rashes spread to his entire body especially his face	Not reported
Abbas, M. (19) (2014)	54/F	500 mg TDS	severe progressive pustular psoriasis on 5 fingers	2 days after taking cephalexin	Not reported	pustule eruption, extensive blisters and peeling	1 wk.
Mattew Dacunha. (7) (2018)	35/F	500 mg QID	Staphylococcal Infection in left forearm	Not reported	left forearm, on the antecubital and popliteal fossa	plaques on the left forearm, erythema, and papules on the antecubital and popliteal fossa along with tender and itching	2 wks.
Our Case (2020)	12/M	powder 500mg TDS	Left leg ulcer	10 days after taking cephalexin	around the wound	Itching, urticaria lesions, Erythematous and urticaria lesions progressively spread to other limbs, trunk, face, and neck	8 days

M: Male, F: Female, TDS: Three times a day, QID: Four times a day,

References:

1. Lockwood SJ, Saavedra AP. Chapter 6 - Cutaneous Reactions to Drugs. In: Khan DA, Banerji A, editors. Drug Allergy Testing: Elsevier; 2018. p. 53-72.
2. Beylot C, Bioulac P, Doutre MS. [Acute generalized exanthematic pustuloses (four cases) (author's transl)]. Annales de dermatologie et de venereologie. 1980;107(1-2):37-48.
3. De A, Das S, Sarda A, Pal D, Biswas P. Acute Generalised Exanthematous Pustulosis: An Update. Indian J Dermatol. 2018;63(1):22-9.
4. Mohaghegh F, Jelvan M, Rajabi P. A case of prolonged generalized exanthematous pustulosis caused by hydroxychloroquine-Literature review. Clin Case Rep. 2018;6(12):2391-5.
5. Halevy S. Acute Generalized Exanthematous Pustulosis. In: Shear NH, Dodiuk-Gad RP, editors. Advances in Diagnosis and Management of Cutaneous Adverse Drug Reactions: Current and Future Trends. Singapore: Springer Singapore; 2019. p. 105-22.
6. Saissi EH, Beau-Salinas F, Jonville-Bera AP, Lorette G, Autret-Leca E. [Drugs associated with acute generalized exanthematic pustulosis]. Annales de dermatologie et de venereologie. 2003;130(6-7):612-8.
7. DaCunha M, Moore S, Kaplan D. Cephalexin-induced acute generalized exanthematous pustulosis. Dermatology Reports. 2018;10(2).
8. Shinde AJ, Patil MS, More HN. Formulation and evaluation of an oral floating tablet of cephalexin. Indian J Pharm Educ Res. 2010;44(3):243-52.
9. Derrick CW, Jr., Reilly K. The role of cephalexin in the treatment of skin and soft-tissue infections. Postgraduate medical journal. 1983;59 Suppl 5:43-6.
10. Macy E, Contreras R. Adverse reactions associated with oral and parenteral use of cephalosporins: a retrospective population-based analysis. Journal of Allergy and Clinical Immunology. 2015;135(3):745-52. e5.
11. Cunha BA. Cephalexin remains preferred oral antibiotic therapy for uncomplicated cellulitis. The American journal of medicine. 2008;121(11):e13.
12. Holscher CM, Mauck SK, Armstrong L, Buchanan JA. Man with Rash and Nausea. Annals of emergency medicine. 2011;58(6).
13. 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.
14. Kley C, Murer C, Maul JT, Meier B, Anzengruber F, Navarini AA. Rapid Involution of Pustules during Topical Steroid Treatment of Acute Generalized Exanthematous Pustulosis. Case Reports in Dermatology. 2017;9(1):135-9.
15. Chaudhry SB, Veve MP, Wagner JL. Cephalosporins: A Focus on Side Chains and beta-Lactam Cross-Reactivity. Pharmacy (Basel, Switzerland). 2019;7(3).
16. Griffith RS. The pharmacology of cephalexin. Postgraduate medical journal. 1983;59 Suppl 5:16-27.
17. Murray KM, Camp MS. Cephalexin-induced Stevens-Johnson syndrome. The Annals of pharmacotherapy. 1992;26(10):1230-3.
18. Arroyo MP, Heller P, Pomeranz MK. Generalized pustules in a healthy woman. Journal of drugs in dermatology: JDD. 2002;1(1):63-5.
19. Abbas M, Holfeld K, Desjardins D, Zimmer J. Pustular psoriasis complicated with acute generalized exanthematous pustulosis. Journal of dermatological case reports. 2014;8(2):42.