

Case Report:

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 may appear after using certain medications, such as cephalexin. This disease is characterized by non-follicular sterile pustules, erythematous, urticaria, fever over , and leukocytosis. Cephalexin belongs to the family of β -lactam antibiotics, which are widely used to treat infections. However, cephalexin skin sensitivities have been reported rarely. Herein, in this case, we aimed to report a patient presented with AGEP due to cephalexin usage.

Case Presentation: A 12-year-old boy presented with warm skin lesions that gradually appeared on the limbs, trunk, face, and neck after using cephalexin powder on his left leg injury. Because of 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.

Conclusions: Cephalexin is one of the antibiotics that doctors and patients consider when there is a possibility of infection. AGEP is a rare but severe reaction that can manifest as skin rashes in any age and sex following the use of cephalexin, so the patient should be careful when using this antibiotic.

1. Introduction

A

cute 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 non-follicular sub-corneal pustules

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[2]. AGEP occurs in one to five cases per million people per year [3]. Although AGEP often affects middle-aged adults, it can occur at any age. Both sexes (with an insignificant prevalence in women) would be affected. The AGEP mortality rate is about 5% [1].

AGEP symptoms include pimples, which appeared on the face or areas of the skin folds and spread within 24 hours, although late symptoms have been mentioned up to 3 weeks after taking the drug. The ebullition of pustular has been seen after post-pustular desquamation. Severe cases of AGEP may appear with unusual lesions and conjunct pussy pimples, leading to extensive surface erosion and redness on the skin, potentially similar to Stevens-Johnson Syndrome (SJS)/ Toxic Epidermal Necrolysis (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 ($>38^{\circ}\text{C}$) and leukocytosis (neutrophil/mL $7000<$) are usually presented with mild eosinophilia. Visceral involvement is rare [4].

AGEP is 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], rubbed on the skin [9] or injected parenterally [10]. Some studies have shown that parenteral use of cephalexin has more side effects than oral use, but this effect has not been proven yet [10, 11]. There are few reports about AGEP as one of the uncommon side effects of cephalexin. According to these reports, after a few days of taking cephalexin, the symptoms of AGEP appear as erythema and pustules in different parts of the body. By discontinuing cephalexin, the symptoms have been improved [7, 12]. In this case, we 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.

2. Case Presentation

A 12-year-old boy was referred to the pediatric clinic with a complaint of 10-d history of skin lesions and itching throughout the body (Figure 1) and having a 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 20 days ago.

The patient used cephalexin capsule powder 500 mg on his wound for 48 hours, 3 times a day. About 10 days later, when itching and urticaria lesions appeared at the wound site, he used hydroxyzine syrup 5 mL twice 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°C (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 (Figure 2). Other examinations were normal.

Laboratory tests did not show any abnormalities except for leukocytosis ($13000\text{ mm}^3/\text{L}$), 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 2400 mg/day, fexofenadine hydrochloride 120 mg/day, loxoprofen sodium 60 mg/day, and an ointment, including difluprednate and hydrocortisone, were prescribed. After a while, his fever subsided. Approximately 8 days after, urticaria and pustular lesions were improved. After two weeks, all the laboratory tests were normal.

3. Discussion

AGEP is a self-limiting reaction [13], and the role of genetics in its development and appearance is unclear [14]. It is 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 challenging to diagnose AGEP disease from generalized pustular psoriasis, but the presence of eosinophils, necrotic keratinocytes, and vascular excretion in the



Figure 1. Subepidermal and intraepidermal postural lesions

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absence of fragile blood vessels is good evidence for AGEP diagnosis. While in generalized pustular psoriasis, 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 help differentiate between AGEP and generalized pustular psoriasis [4]. Another way to diagnose AGEP is using 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 cri-

teria) is a practical tool for diagnosis [5]. This validation score consists 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, discontinuation of causative medications, topical corticosteroids, and antipyretics could be helpful [14]. Symptoms usually go away in a few days, but older people or patients with immunodeficiency with a widespread manifestation of skin rash may still need to be hospitalized to receive fluid and electrolyte support [3].



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Figure 2. Crusted wound on the left leg

Cephalexin is the first generation of cephalosporin antibiotics from the β -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 because of their widespread clinical use and are well tolerated among antibiotics. About 1%-3% of people have a his-

tory 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 eosinophilia, fever, anaphylaxis, angioedema, rhinitis, and bronchospasm. These symptoms can approximately 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 effects [7]. Cephalexin makes skin lesions such as violaceous macular rash, erythematous, and numerous extensive 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 fifth 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 (Table 1). 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 on his own on his left foot ulcer. Of the 4 cases reported, three were females [7, 18, 19], and one was male [12], such as our case, indicating

Table 1. Description of five cases of cephalexin-induced acute generalized exanthematous pustulosis

Authors	Age (y)/ 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	Four 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 five fingers	Two days after taking cephalexin	Not reported	Pustule eruption, extensive blisters and peeling	1 wk
Matthew Da-cunha. [7] (2018)	35/F	500 mg QID	Staphylococcal Infection in the 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 wk
Our case (2020)	12/M	Powder 500 mg TDS	Left leg ulcer	Ten days after taking cephalexin	Around the wound	Itching, urticaria lesions, Erythematous and urticaria lesions progressively spread to other limbs, trunk, face, and neck	8 d

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

more females involvement. In the 2 previous patients [12, 18] and 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 cephalixin. These times include two days after the first use of cephalixin [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 involvement has been reported following cephalixin use, which could be a positive point. In most cases studied, as in our case, the bacterial culture result was negative [7, 18, 19], and the CBC result shows leukocytosis [19].

The first treatment that has been considered in all cases is the discontinuation of cephalixin. The second step is supportive corticosteroid 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 included acetaminophen, fexofenadine hydrochloride, loxoprofen sodium, and an ointment, including difluprednate and hydrocortisone, which improved the patient's condition 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 primarily 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.

4. Conclusion

Cephalixin is one of the antibiotics that doctors and patients consider when there is a possibility of infection. AGEP is a rare but severe reaction that can develop into skin rashes in any age group and gender following the use of cephalixin. So the patients should 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 cephalixin is the first practical step in treating the affected patient. It is unnecessary to take

steroids because AGEP is self-limiting but can effectively increase the speed of improving symptoms.

Ethical Considerations

Compliance with ethical guidelines

All ethical principles are considered in this article. The participants were informed of the purpose of the research and its implementation stages. They were also assured about the confidentiality of their information and were free to leave the study whenever they wished, and if desired, the research results would be available to them. Written consent has been obtained from the subjects. principles of the Helsinki Convention were also observed.

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Authors' contributions

All authors equally contributed to preparing this article.

Conflicts of interest

The authors declared no conflict of interest.

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