Journal of Pakistan Association of Dermatologists. 2024;**34(3)**:785-789.

Case Report

Acute generalized exanthematous pustulosis suspected induced by cefadroxil after receiving the vaccine Covid-19: A case report

Cut Putri Hazlianda, M. Ridlo

Department of Dermatovenereology, Faculty of Medicine, Universitas Sumatera Utara, Indonesia.

Abstract Acute Generalized Exanthematous Pustulosis (AGEP) is a rare skin condition that is typically triggered by drug reactions, particularly antibiotics, but can also arise from infections or vaccinations. Its primary symptom is the sudden appearance of sterile pustules with erythematous, accompanied by systemic symptoms such as fever. Unless complicated by secondary infection, AGEP usually resolves spontaneously and has a favorable prognosis.

Key words
AGEP; Cefadroxil; Corona vaccine; Vaccine Covid-19.

Introduction

Acute Generalized Exanthematous Pustulosis (AGEP), also called pustular drug rash or pustular eruption or toxic pustuloderma is a rare inflammatory dermatological and mucosal condition. The disorder is characterized by the sudden onset of multiple sterile pustules and erythema on the skin and mucous membranes. Typically, AGEP initially manifests on the face or skin folds and within a few hours it spreads to the trunk and lower extremities. The primary symptoms of AGEP are the presence of pustules and redness, and mild burning and minimal itching may accompany the condition.[1-3] According to medical literature, the reported incidence of AGEP is 1-5 cases per 1 million population per year. However, many cases may go unreported.[3]

Manuscript
Received on: April 27, 2023
Revised on: February 14, 2024
Accepted on: April 10, 2024
Address for correspondence
Dr. Cut Putri Hazlianda
Departmen of Dermatology and Venereology,
Universitas Sumatera Utara, Indonesia.
Email: cut.putri@usu.ac.id

The initial case report of AGEP was documented by Campbell and Furtado in Brazil, who described a female patient who developed AGEP after taking ampicillin.[4] A subsequent retrospective study conducted by Lin *et al*. in Taiwan from 2006 to 2012 investigated 74 cases of Severe Cutaneous Adverse Reactions (SCARs). It revealed that penicillin and cephalosporin antibiotics were the most frequently implicated agents in AGEP and SJS/TEN cases.[5] Study conducted by Stingeni *et al*. showed the incidence of AGEP was 24 hours after the administration of cephalosporin antibiotics in COVID-19 patients.[6]

The WHO report in April 2021 on the incidence of the adverse event following immunization (AEFI) from Sinovac occurred in Mexico. Of the 17,027 cases of AEFI there were 117 cases from the Sinovac vaccine.[7] Although case reports of vaccine-induced AGEP are limited, Kang *et al*. first reported a case of AGEP occurring three weeks after receiving the COVID-19 vaccine (ChAdOx1-nCoV-19 vaccine, AZD1222). However, the mechanism underlying this occurrence is still unknown.[8]

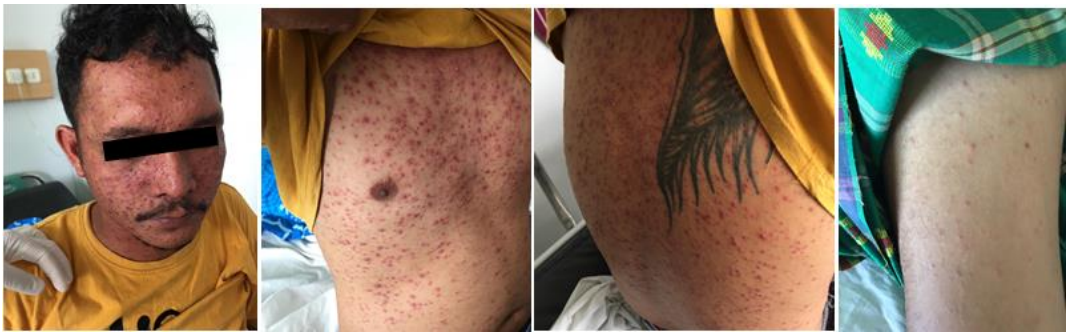

Figure 1 The patient's condition on the first day of hospitalization.

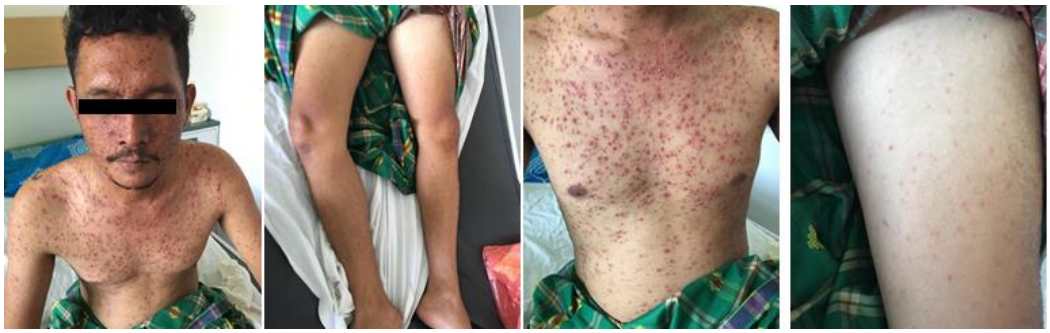

Figure 2 The condition of the patient on the second day of hospitalization.

Case report

A 31-year-old patient presented in the Department of Dermatology and Venereology in the Universitas Sumatera Utara Hospital with the chief complaint of red, itchy and painful rashe all over the body for past three days. The rash initially appeared on the face and spread over the entire body. The patient had a recent history of receiving the CoronaVac/Sinovac vaccine for COVID-19, six days before hospital admission. One day after vaccination, the patient developed a flu and took cefadroxil. The day after taking the medication, redness appeared, spreading over the next day. The patient also reported symptoms of nausea and vomiting. There was no history of respiratory tract infection before or after vaccination.

On dermatological examination pustules, papules, discrete and some confluent crusts, with erosions on the face, thoracic, abdominal, vertebral, and femoral regions. The mucosal examination was normal **(Figures 1,2)**. Laboratory examination revealed neutrophilia (77.8 %), elevated triglycerides (245 mg/dl), increased SGOT (68 U/L), and negative human immunodeficiency virus (HIV) serology. The KOH examination of skin smear was negative. Pustule cultures showed neutrophils, PMN leukocytes, and no bacteria were found. Biopsy was not performed because the patient refused the procedure. The EuroSCAR scoring system got a definite AGEP with a final score of 8 **(Table 1).**

Table 1 AGEP scores in patients according to the EuroSCAR study group.

Morphology	
Pustules: Typical	+2
Erythema: Typical	+2
Distribution/pattern: Typical	+2
Postpustular desquamation: No/insufficient	0
Course	
Mucosal involvement: No +	0
Acute onset (<10 days): Yes +	0
Resolution <15 days: Yes +	0
Fever >38°C: Yes	+1
Polymorphonuclear neutrophils >7,000/mm^3: Yes	+1
Histology	
No histology	0
Total	8

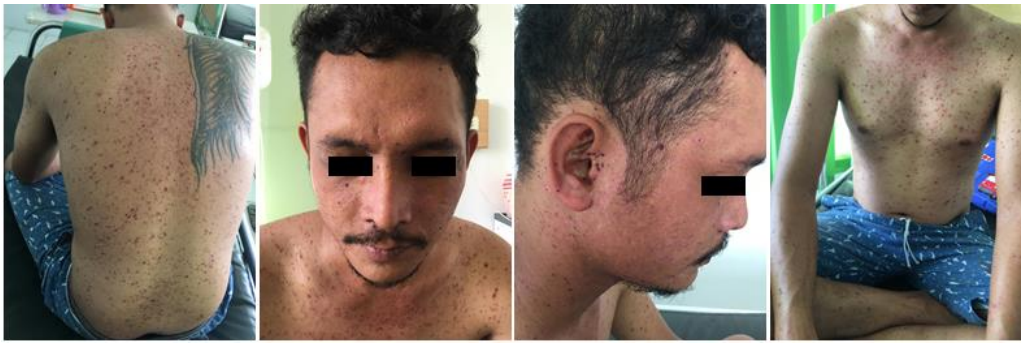

Figure 4 The patient's condition on the sixth day of hospitalization.

Differential diagnosis of this patient is AGEP induced by cefadroxil, Malassezia folliculitis, and drug reaction with eosinophilia and systemic symptoms (DRESS). Based on history, physical examination and laboratory examination, the patient was diagnosed with AGEP suspected to be induced by cefadroxil.

The patient was hospitalized and received oral corticosteroid (methylprednisolone 48 mg/day) and ranitidine injection. Steroids were gradually reduced, cetirizine 10 mg/day, topical antibiotic (gentamicin sulfate 0.1%), urea moisturizer and moist compresses of 0.9% NaCl were applied for 20 minutes every four hours over wet and red lesions.

On the sixth day of hospitalization, the patient showed a significant clinical improvement **(Figure 4)**. The patient's prognosis is quo ad vitam Bonam, quo ad functionam Bonam, quo ad sanactionam Bonam.

Discussion

According to the literature, AGEP is characterized by the appearance of sterile pustules, either follicular or non-follicular, on erythematous skin, often accompanied by fever and flu like symptoms along with hyper acute onset. While the condition is typically self-limiting, skin eruption may persist for up to 9 days, with a mean duration of 4-14 days before resolving spontaneously and leading to desquamation. Mucous membrane involvement is rare, occurring in approximately 20% of cases, and typically affects only one mucosal area.[1,3,4] Some cases of AGEP may also present with lymphadenopathy. To establish a diagnosis of AGEP, the EuroSCAR study utilizes validation scores based on clinical and histopathological criteria, which categorize patients into definite, probable, possible, or non-AGEP cases.[9,10]

In this case, the patient developed fever one day after receiving the COVID-19 vaccine, followed by a red rash one day after taking cefadroxil (two days after the vaccine). Cefadroxil is a first-generation cephalosporin effective against gram-positive cocci, including streptococci, pneumococci and staphylococci. The antimicrobial spectrum of first-generation cephalosporins is mainly active against gram-positive bacteria. The adverse reaction that occurs most frequently to cefadroxil is a hypersensitivity reaction that resembles a penicillin hypersensitivity reaction. Other adverse reactions include nausea, vomiting, and nephrotoxicity.[11]

In this case, the patient was diagnosed differently with Malassezia folliculitis and DRESS. DRESS is a grave drug-induced reaction that is distinguished by skin rash, fever, and impairment of inner organs. The clinical features of DRESS syndrome bear resemblance to those of other drug-induced allergic skin eruptions. In DRESS, skin lesions usually

appear 2 to 8 weeks after taking the drug. In addition, lymphadenopathy, internal organ abnormalities, and abnormal hematological examinations were also found.[1,15]

In this instance, the 20% KOH test yielded a negative result. Malassezia folliculitis is a persistent infection of pilosebaceous follicles caused by Malassezia sp. It is frequently seen in adolescents and is marked by the emergence of erythematous papules and pruritic perifollicular pustules without constitutional symptoms, typically on the upper body and less frequently on the face. High temperatures can elevate the sebum the skin produces, creating an ideal habitat for Malassezia sp. Treatment generally involves topical antifungal shampoo or systemic antifungal therapy.[16] presence of fever and flu like symptoms along with hyper acute onset differentiates AGEP from malassezia.

In the patient, the main approach to therapy is to discontinue the suspected causative drugs and administer topical and oral corticosteroids. Since AGEP is a condition that resolves on its own, targeted therapy is typically not required. The immediate cessation of the suspected drug is of critical importance. Symptomatic relief can be achieved with antipyretics or antihistamines. Antibiotics are only prescribed when there is a confirmed diagnosis of infection. In most cases, topical and systemic corticosteroids can reduce inflammation and alleviate irritation.[1,3,9]

The prognosis for AGEP is generally good, particularly following discontinuation of the suspected causative agent, unless there is an accompanying secondary infection of the lesions or among older patients with a high fever.[9,10]

Conclusion

This study showcases the case of a 31-year-old male patient who presented with AGEP, which was suspected to be induced by cefadroxil. The patient also recently received the first dose of the COVID-19 vaccine. Although cefadroxil is suspected as the causative agent, in this case, the possibility of a vaccine being the causative agent cannot be ruled out.

Declaration of patient consent The authors certify that they have obtained all appropriate patient consent.

Financial support and sponsorship None.

Conflict of interest Authors declared no conflict of interest.

Author's contribution

CPH: Diagnosis and management of the case, critical review, has given final approval of the version to be published.

MR: Identification and management of the case, manuscript writing, has given final approval of the version to be published.

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