

Received: 2020.06.18

Accepted: 2020.09.09

Available online: 2020.09.16

Published: 2020.10.24

Delayed Presentation of Acute Generalized Exanthematous Pustulosis Following Treatment with Cefepime in a Patient with COVID-19 without the Use of Hydroxychloroquine

Authors' Contribution:

Study Design A
Data Collection B
Statistical Analysis C
Data Interpretation D
Manuscript Preparation E
Literature Search F
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Conflict of interest: None declared

Patient: Male, 78-year-old
Final Diagnosis: Acute generalized exanthematous pustulosis (AGEP)
Symptoms: Rash
Medication: —
Clinical Procedure: —
Specialty: Allergology • Infectious Diseases

Objective: Rare disease

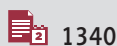
Background: Acute generalized exanthematous pustulosis (AGEP) is a rare exanthem characterized by the abrupt onset of numerous small, non-follicular, sterile pustules arising on an erythematous base. AGEP is often associated with medications; however, it has also been connected to various viral infections including cytomegalovirus, parvovirus B19, and Epstein-Barr virus. Coronavirus disease 2019 (COVID-19) has been associated with a variety of skin findings, including erythematous or patchy rash, urticaria, hives, blisters, petechiae, livedo reticularis, and even AGEP in a patient undergoing treatment with hydroxychloroquine.

Case Report: A 78-year-old man with a past medical history of benign prostatic hyperplasia, coronary artery disease, and atrial fibrillation presented with septic shock secondary to a urinary tract infection. On day 7 of treatment with cefepime, he became febrile and developed a pustular rash and persistent hypotension without any respiratory symptoms. Subsequently, he was diagnosed with COVID-19. Skin biopsy of the rash revealed AGEP.

Conclusions: AGEP is an uncommon cutaneous eruption often triggered by medications and viruses. AGEP is thought to be mediated by pro-inflammatory cells and cytokines. This report describes an unusual presentation of AGEP following treatment with cefepime for a urinary tract infection in a 78-year-old man who was found to be positive for SARS-CoV-2 infection, but was not treated with hydroxychloroquine. Although AGEP has been described in association with some viral infections, it is more commonly a drug-associated dermatosis, commonly seen during treatment with antibiotics. As in this case, AGEP usually resolves after discontinuation of the offending antibiotic.

MeSH Keywords: Acute Generalized Exanthematous Pustulosis • COVID-19 • Severe Acute Respiratory Syndrome • SARS Virus • Cephalosporins • Exanthema

Full-text PDF: <https://www.amjcaserep.com/abstract/index/idArt/926901>



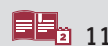
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Background

Acute generalized exanthematous pustulosis (AGEP) is a rare exanthem characterized by the abrupt onset of numerous small, non-follicular, sterile pustules arising on an erythematous base. AGEP is usually associated with medications, especially aminopenicillins, diltiazem, and antimalarials like hydroxychloroquine [1–3]. However, it has also been connected to certain viral infections including cytomegalovirus, parvovirus B19, and Epstein-Barr virus [1,2]. As coronavirus disease 2019 (COVID-19) continues to dominate headlines, many reports are coming forward with associated skin manifestations, including petechial rashes, vesicles, chilblains, and urticaria [4–6]. This report is of a case of AGEP following treatment with cefepime for a urinary tract infection in a 78-year-old man who was positive for SARS-CoV-2 infection but had not undergone hydroxychloroquine treatment.

Case Report

A 78-year-old man with a past medical history of benign prostatic hyperplasia, coronary artery disease, and atrial fibrillation presented to the emergency department from a nursing facility due to leukocytosis, worsening renal function, and hyperkalemia. He was admitted to the Intensive Care Unit (ICU) due to hemodynamic instability and septic shock secondary to a *Pseudomonas aeruginosa* urinary tract infection. He was started on cefepime, and briefly required vasopressor support. On day 7 of admission, he spiked a fever of 38.3°C and

developed a pustular rash on an erythematous base covering his upper extremities and trunk (Figure 1). There was no mucosal involvement.

Laboratory studies were significant for leukocytosis with neutrophilia (8170 neutrophils/ μ l; normal range, 1800–7500 neutrophils/ μ l), and an elevated C-reactive protein level (4.15 mg/dL; normal range, 0–1 mg/dL). A chest X-ray (CXR) was obtained, which did not show any acute cardiopulmonary abnormality. Repeated blood, urine, and pustule cultures for bacteria were negative. The following day, the patient was persistently hypotensive without any other symptoms. Repeated CXR showed new-onset bilateral interstitial opacities and consolidation. Given that the patient was admitted from a nursing facility, as well as his new CXR findings, he was tested for COVID-19 via the SARS-CoV-2 RNA nasopharyngeal swab followed by real-time reverse transcription polymerase chain reaction (RT-PCR) and found to be positive. He did not show any signs of respiratory distress or require supplemental oxygen, and was treated supportively.

A skin biopsy of the rash showed papillary dermal edema, and subcorneal/intracorneal pustules. Within the surrounding dermis, there was mixed inflammatory infiltrate composed of lymphocytes, neutrophils, and rare eosinophils (Figure 2). Based on the EuroSCAR study group criteria, our patient had a score of 12, indicating a definite diagnosis of AGEP [3]. At this point, cefepime was discontinued, and he was treated symptomatically with topical emollients, which resulted in expedient resolution of the exanthem within a few days, followed by post-pustular desquamation.



Figure 1. Clinical presentation. Acute generalized exanthematous pustulosis with numerous pinpoint pustules on edematous erythema of the left upper extremity (A), left posterior forearm (B), and left distal posterior triceps (C).

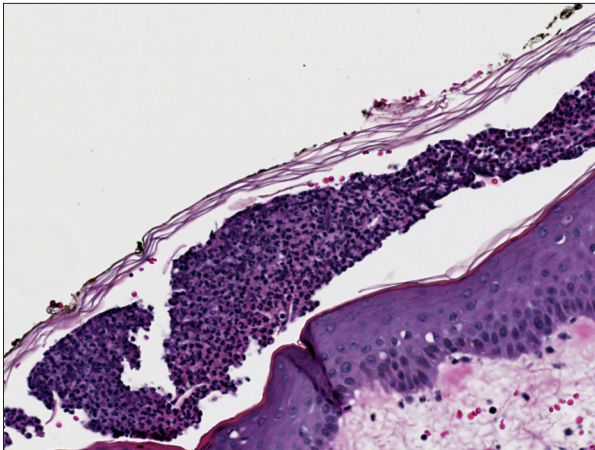


Figure 2. Histopathology. Acute generalized exanthematous pustulosis. The diagnostic histological features of acute generalized exanthematous pustulosis (AGEP) included intraepidermal neutrophils and exudate that formed pustules and papillary dermal oedema with neutrophils and eosinophils. Magnification, 40x. Stain, hematoxylin and eosin (H&E).

Discussion

AGEP is an acute pustular reaction characterized by the rapid onset of tens to hundreds of pinpoint, sterile, non-follicular pustules on a background of edematous erythema [3]. It is most commonly caused by medications, but has also been linked to viral infections, spider bites, and mercury [1–3]. The time period from drug administration to onset of eruption is typically within the first 48 hours, with antibiotics having a median of 24 hours [2]. It is a self-limiting disease that quickly resolves within 2 weeks after withdrawal of the offending agent [2]. During resolution, there is desquamation with characteristic collarettes of scale [2,3].

Diagnosis is based on clinical presentation and histologic findings. An AGEP validation score was developed by the EuroSCAR study group that includes the following diagnostic criteria: fever ($>38^{\circ}\text{C}$), acute pustular eruption, blood neutrophilia ($>7,000$ neutrophils/ μL), spongiform subcorneal or intraepidermal pustules on skin biopsy, and spontaneous resolution of the pustules in less than 15 days [3]. The histological features of AGEP are characterized by subcorneal pustules, mild spongiosis in the surrounding epidermis, and superficial mixed infiltrate composed of lymphocytes, neutrophils, and occasional eosinophils [2,3]. The main differential diagnoses for AGEP are pustular psoriasis and drug rash with eosinophilia and systemic symptoms (DRESS). Pustular psoriasis is typically associated with a personal or family history of psoriasis, and typically has a slow onset. DRESS is typically associated with a longer latent period of 2 to 6 weeks [2]. In our patient, the lack of personal history of psoriasis, acute onset, and resolution

after discontinuation of cefepime, as well as the histologic features of eosinophils in the mixed infiltrate, helped to distinguish AGEP from pustular psoriasis and DRESS. Based on the EuroSCAR criteria and histologic findings, our patient fulfilled the diagnostic criteria for AGEP.

As previously mentioned, antibiotics typically induce AGEP to develop within 24 hours after drug administration; however, our patient went on to develop AGEP 7 days after starting cefepime [2]. He was, however, diagnosed with COVID-19 on the same day that his fever began and his rash appeared. To the best of our knowledge, this is the second reported case of AGEP in a patient with COVID-19 [7]. In the other reported case, the patient developed AGEP 18 days after hydroxychloroquine was initiated as treatment for COVID-19 infection [7]. In regards to our patient, we hypothesize that his vigorous immune response to COVID-19, coupled with concurrent cefepime use, may have triggered the appearance of AGEP.

The pathophysiology of AGEP is only partially understood. Studies suggest that AGEP is a T cell-mediated neutrophilic inflammatory response, involving drug-specific T cells (CD4+ and CD8+), Th17 cells, inflammatory cytokines, and chemokines [2,3,8]. Th17 cells produce the pro-inflammatory cytokines IL-17 and IL-22, which play an important role in host defense by recruiting neutrophils and macrophages to infected tissues [8]. One report noted patients with AGEP had a markedly higher percentage of Th17 cells when compared with healthy controls [8]. There may also be a genetic component to the development of AGEP through mutations in the IL-36 receptor antagonist (IL36RN) gene [9]. However, patients with AGEP and IL36RN gene mutations are more likely to have lip/oral involvement, which was not seen in our patient [9].

In COVID-19, the antiviral immune response is crucial to eliminating the invading virus, and researchers are finding that pro-inflammatory subsets of T cells (including Th17 and other CD4+ T cells, as well as CD8+ T cells) are likely responsible for the severe immune-related injury to various organ systems [10]. It is thought that a robust and persistent immune response may lead to an overproduction of inflammatory cytokines, causing damage to host tissues [10]. Reports have shown that, in the later stages of COVID-19 infection, cytokine storm is likely a major cause of disease progression [6,10]. In addition, the elderly tend to exhibit chronic low-grade inflammation which develops from the continual production of inflammatory mediators and cytokines, thereby lowering the threshold to develop cytokine storm during COVID-19 infection [11]. Since AGEP usually develops 24 hours after cephalosporin use, we theorize that our patient's vigorous immune response to COVID-19 infection, combined with cefepime use, may have contributed to the delayed development of AGEP.

As information regarding the manifestations of COVID-19 continues to be discovered, it is possible that cutaneous manifestations were initially overlooked. In our patient, it is likely that cefepime induced the manifestation of AGEP. However, it is possible that the development of AGEP was multifactorial. We theorize that the combination of cephalosporin exposure, genetic predisposition, and the production of pro-inflammatory cells and cytokines induced a vigorous immune response leading to the delayed development of AGEP. It is our hope that sharing this case may be of benefit to providers when dealing with rashes during this pandemic.

Conclusions

AGEP is an acute pustular eruption that is typically induced by medications and viruses. This report described an unusual

presentation of AGEP following treatment with cefepime for a urinary tract infection in a 78-year-old man who was found to be positive for SARS-CoV-2 infection, but was not treated with hydroxychloroquine. Although AGEP has been described in association with some viral infections, it is more commonly a drug-associated dermatosis, commonly seen during treatment with antibiotics. As in this case, AGEP usually resolves after discontinuation of the offending antibiotic.

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Conflict of interest

None.

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