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Case Report

# Macrolide Antibiotic-Induced Acute Generalized Exanthematous Pustulosis in an Epileptic Patient on Phenytoin Therapy

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## ABSTRACT

Acute Generalized Exanthematous Pustulosis (AGEP) is a rare and severe cutaneous adverse reaction characterized by the abrupt onset of widespread sterile pustules on an erythematous base. This is associated with medications, including antiepileptic drugs, phenytoin, and antibiotics such as beta-lactams and macrolides. This is a rare case where a macrolide antibiotic is reported to induce AGEP in an epileptic patient who was on phenytoin therapy. The patient, at the age of 25, was taking phenytoin for the past two years to subside epileptic symptoms. In this period, he has never reported any complications related to AGEP. Including macrolide antibiotics in his prescription aggravated the symptoms of AGEP within a few days. The primary course of action involved immediate withdrawal of both the drugs i.e. phenytoin and macrolide antibiotic, and symptomatic treatment.

**Keywords:** Exanthematous Pustulosis, Cutaneous, Macrolide, Phenytoin.

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## INTRODUCTION

In 1980, the first reported case of Acute Generalized Exanthematous Pustulosis (AGEP) marked the inception of its recognition as a distinct disease entity, differentiating it from pustular psoriasis. Subsequently, Baker and Ryan, in 1986, elucidated the characteristics of AGEP in a cohort of five patients experiencing medication-related pustular eruptions of acute onset. Notably, these patients had no prior history of psoriasis, leading to the establishment of the term Acute Generalized Exanthematous Pustulosis (AGEP), commonly associated with cutaneous side effects. The implicated causative agents included antibiotics such as beta-lactams and macrolides.[1]

A hallmark feature of AGEP is the emergence of pustules with erythema, accompanied by an elevation in body temperature and a neutrophilic count exceeding 5000/mL. Spontaneous resolution typically occurs within 15 days following the discontinuation of the precipitating drug.[2] Manifestations of fever and pustulosis, often accompanied by leukocytosis, are observed within 48 hr after administering the causative agent. In some instances, mucous membranes and systemic organs may become involved, contributing to the severity of the pathological condition.

Histopathological studies reveal pustules with papillary dermal and intracorneal, subcorneal, and/or intraepidermal edema containing neutrophils and eosinophils. The primary therapeutic objective is the swift discontinuation or cessation of the implicated drug or medication. Additionally, comprehensive supportive care is a crucial component of the management strategy for individuals with AGEP. Supportive care aims to achieve two main objectives: first, to prevent the development of secondary infections, and second, to alleviate the symptoms associated with the skin eruption. Rigorous hygiene practices, including gentle cleansing of affected areas and meticulous wound care, are integral to minimizing the risk of infection. In addition to general supportive measures, the use of potent topical steroid preparations is often considered. Topical steroids can help mitigate inflammation, reduce itching, and promote the healing of the affected skin. These medications work by suppressing the local immune response and alleviating the signs and symptoms

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of AGEP. Vigilance in managing AGEP is crucial, considering its rapid onset and potential systemic involvement, necessitating a comprehensive approach to patient care.

## CASE REPORT

A 25-year-old male patient was admitted to the dermatology department with primary complaints of fever reaching 101°F, accompanied by widespread itching and a burning sensation throughout his body. The oral involvement was significant, rendering him unable to consume food. The patient reported lesions that initially appeared as fluid-filled and progressed to pustules over the past three months, causing persistent itching and burning sensations. The patient has a history of seeking treatment for this condition at other healthcare facilities. Moreover, the patient has a documented medical history of epilepsy and has been receiving phenytoin treatment for the past two years. Notably, preceding the onset of skin lesions, the patient had recently taken macrolide antibiotics.

### Systemic examination

It revealed normal cardiac sounds (S1, S2) in the cardiovascular system. The respiratory system exhibits bilateral air entry with normal vesicular breath sounds. The abdomen appeared scaphoid. Central Nervous System (CNS) examination showed no focal neuronal deficit.

### Skin Examination

The investigation revealed erosions, erythema with purulent discharge, and crust present throughout the body, except for the palms and legs (Figure 1). Oral examination exhibited whitish plaques, erosions, and erythema on the buccal mucosa and the hard palate.

### Patient's vital signs and laboratory results

Temperature: Afebrile; Pulse Rate (bpm): 92; Respiratory Rate (cpm): 22; Blood Pressure (mmHg): 110/80; Hemoglobin (Hb): 10.2 gm/dL; White Blood Cells (WBC): 3200 cells/cumm; Red Blood Cells (RBC): 3.9 million cells/cumm; Platelets: 3.4 lakhs; Aspartate Aminotransferase (AST): 125 IU/L; Alanine Aminotransferase (ALT): 518 IU/L; Albumin: 2.6 g/L; Blood Urea Nitrogen (BUN): 40 mg/dL.

### Clinical Diagnosis

The patient is diagnosed with a lichenoid drug eruption, characterized by damage with neutrophil infiltration between the dermis and epidermis.

### Ultrasonography (USG) Findings

The abdominal ultrasound reveals no abnormalities in the abdomen, liver, kidney, gallbladder, spleen, or prostate. This ruled out any structural issues in the internal organs.

### Microbiological Testing

Laboratory tests do not detect the presence of any clinically significant pathogens. This suggests that the patient's symptoms were likely not due to an infectious agent.

Based on these findings, the patient was diagnosed with Acute Generalized Exanthematous Pustulosis.

## DISCUSSION

The diagnosis of drug-induced skin rashes relies on the evaluation of circumstantial evidence. Despite sharing clinical and histological features, distinguishing between Acute Generalized Exanthematous Pustulosis (AGEP) and generalized psoriasis is facilitated by parameters proposed by BEYLOT in 1980. These criteria serve to differentiate between the two conditions and, importantly, help in distinguishing them from various other

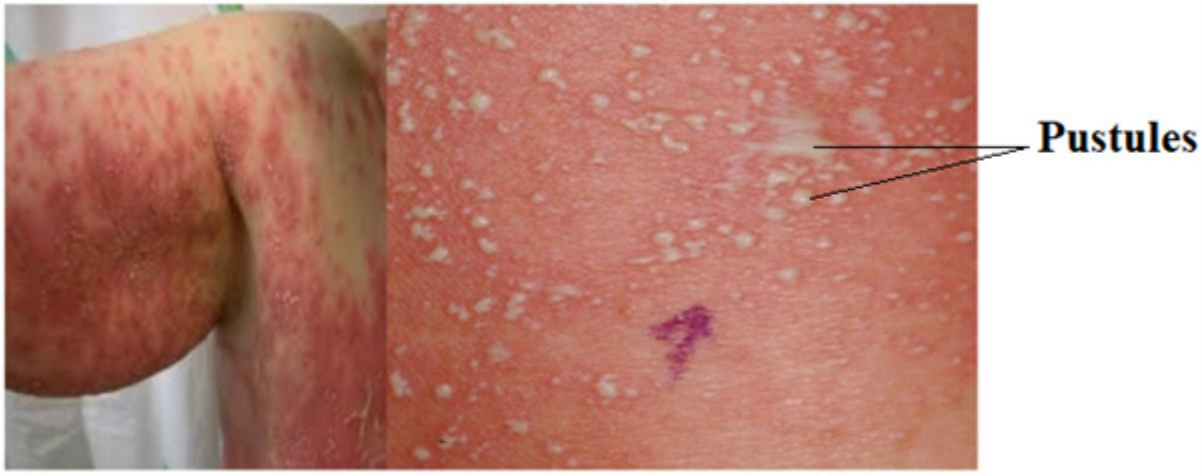


**Figure 1:** The pus-filled lesions (Pustules) covering the whole body of the patient show Acute Generalized Exanthematous Pustulosis. (https://diseaeseshows.com/acute_generalized_exanthematous_pustulosis/)

pustular dermal conditions such as Sneddon Wilkinson Disease, Toxic Epidermal Necrosis, Pustular Miliaria, contact with pustular dermatitis, and pustular skin infections.[3] By applying these specific criteria, clinicians can refine their diagnostic approach, ensuring accurate identification and differentiation of drug-induced rashes from other dermatological conditions with similar manifestations.

Four criteria have been proposed to facilitate the differentiation between Acute Generalized Exanthematous Pustulosis (AGEP) and pustular psoriasis: (a) Adverse Drug Reaction History; (b) Time of Drug Administration; (c) Pustule Duration, and (d) Onset of Fever. In Acute Generalized Exanthematous Pustulosis (AGEP), a rapid onset of fever is typically observed within 24 hr after drug administration. Clinically, AGEP is characterized by diverse eruptions, occurring as a single episode with a quick course of action[4] and lacks arthritis. Conversely, pustular psoriasis exhibits monomorphic eruptions that last longer and tend to recur. Arthritis is observed in only 32% of cases, and drug etiology is rarely implicated.

Within a few hours, clinical symptoms of AGEP spread to the trunk, limbs, and intertriginous parts of the body. Mucous membrane involvement is noted in 25% of cases. Occasionally, the pustules converge, creating a false appearance of a positive Nikolsky's sign. This convergence can lead to misinterpretation, potentially resembling toxic epidermal necrosis or Staphylococcal Scalded Skin Syndrome (SSSS).[5,6]

In this clinical case, the patient's presentation began with clinical symptoms, including a fever of 101°F, accompanied by generalized itching and a burning sensation throughout the body. The severity of the condition led to the patient's inability to consume food due to oral involvement. The skin lesions initially appeared as fluid-filled, progressing to the development of pus, and were associated with persistent itching and burning sensations over the course of three months.

To address the patient's condition, a therapeutic approach was initiated, including the administration of Cefotaxime (1 g IV, twice daily), Levocetirizine (5 mg orally once a day), B-complex supplements, Framycetin (topical application over the lesions), Paracetamol (650 mg orally once a day), and Benzocaine combined with Pheniramine Maleate (as needed, intramuscularly). The inclusion of Cefotaxime, an antibiotic, aimed to combat potential bacterial infections, while Levocetirizine addressed the allergic component by alleviating itching. B-complex supplements were likely provided for nutritional support. Topical Framycetin served as a local antimicrobial application for the skin lesions. Paracetamol was administered for its antipyretic and analgesic properties. Lastly, the combination of Benzocaine and Pheniramine Maleate, administered as needed intramuscularly, suggests a targeted approach for symptom relief, potentially focusing on pain and allergy management. This comprehensive treatment approach reflects a multidimensional strategy aimed at addressing the various aspects of the patient's clinical presentation, including infection control, symptom relief, and nutritional support.

Since no infection was diagnosed, the use of Cefotaxime was not recommended for the patient due to its potential to lower leukocyte levels, which were already low. Also, considering the increased levels of AST and ALT, it is advised to use Paracetamol on as as-needed basis to prevent any further deterioration. The skin of the patient became dry and scaly, therefore, it is recommended to use moisturizers like topical liquid paraffin. The reduced level of hemoglobin, of the patient requires the inclusion of Ferrous Gluconate syrup in their therapeutic regimen.

## CONCLUSION

This case represents a rare occurrence in which a macrolide antibiotic is documented to induce Acute Generalized Exanthematous Pustulosis in a patient undergoing phenytoin therapy. While both macrolide antibiotics and phenytoin have been individually associated with Acute Generalized Exanthematous Pustulosis, the patient had been successfully on phenytoin therapy for the past two years without any complications. The onset of Acute Generalized Exanthematous Pustulosis occurred only after the introduction of the macrolide antibiotic. It remains unclear whether this manifestation is solely attributable to the macrolide antibiotic or results from a combined effect with phenytoin. The recommended course of action for treatment involves the immediate discontinuation of the implicated drug and subsequent symptomatic treatment.

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## CONFLICT OF INTEREST

The authors declare that there is no conflict of interest.

## ABBREVIATIONS

**AGEP:** Acute Generalized Exanthematous Pustulosis; **CNS:** Central Nervous System; **RBC:** Red Blood Cell; **WBC:** White Blood Cell; **Hb:** Hemoglobin; **AST:** Aspartate Aminotransferase; **ALT:** Alanine Aminotransferase; **BUN:** Blood Urea Nitrogen; **SSSS:** Staphylococcal Scalded Skin Syndrome.

## ETHICS APPROVAL AND CONSENT TO PARTICIPATE

The studies involving human participants were reviewed and approved by Ethics Committee of the Varma Hospitals. The patients/participants provided their written informed consent to participate in this study. Written informed consent was obtained

from the individual(s), and minor(s)' legal guardian/next of kin, for the publication of any potentially identifiable images or data included in this article Consent was obtained or waived by all participants in this study.

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