



ACUTE GENERALIZED EXANTHEMATOUS PUSTULOSIS (AGEP) CAUSED BY ANTIBIOTIC POLYTHERAPY: A CASE REPORT

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SUMMARY – Acute generalized exanthematous pustulosis (AGEP) is a rare disease, usually associated with drug intake or infections. It is characterized by generalized acute pustules and non-follicular exanthema together with systemic symptoms. Histologically, it is characterized by a subcorneal intraepidermal spongiform pustule, papillary edema and dermal vasodilatation surrounded by a polymorphous infiltrate of neutrophils, eosinophils and mononuclear cells. The aim of this article is to present current knowledge regarding the etiology and treatment, as well as the clinical and histologic features of AGEP. We present a case of a 50-year-old male patient who was prescribed several antibiotics and developed a drug-related cutaneous adverse effect. Treatment involved rapid identification of the causative agent and its discontinuation together with supportive measures, with resolution of symptoms within two weeks. Early diagnosis and timely treatment result in a favorable outcome and prevent systemic complications.

Keywords: *Acute generalized exanthematous pustulosis; Severe cutaneous adverse reactions, drugs; Antibiotics*

Introduction

The term acute generalized exanthematous pustulosis (AGEP) was first introduced by Beylot *et al.* in 1980 and refers to the acute onset of generalized erythema with dozens to hundreds of sterile non-follicular pustules, which occurs after drug exposure and tends to spontaneously regress and completely resolve upon discontinuation of the causative drug^{1,2}. In most cases, symptoms appear within a few hours, days, or even several weeks after initiating the medication^{2,3}.

Consequently, identifying the responsible drug can be challenging.

We report a case of a patient who developed AGEP after undergoing treatment with multiple antibiotics within a short period.

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Case Report

A 50-year-old male patient was referred to our department with pruritic dermatosis accompanied by fever lasting for five days. The patient reported undergoing a dental procedure (tooth extraction followed by abscess formation, incision, and pus drainage) two weeks prior to the onset of symptoms, when he received the antibiotic doxycycline 100 mg *per os* (PO) twice daily. However, the inflammation worsened and after 2 days of doxycycline treatment, the antibiotic was substituted by a combination of benzylpenicillin 1 million international units (MIU) intramuscularly (IM), gentamicin 120 mg IM, and metronidazole 400 mg PO. The following day, the patient developed high fever of up to 38.9 °C and subsequently maculopapular exanthema on the trunk, as well as upper and lower limbs. He presented to the emergency department and was given methylprednisolone 60 mg IM and desloratadine 5 mg PO.

Five days after the onset of fever, the patient presented with disseminated non-follicular pustules 1-2 mm in diameter on an erythematous base (Fig. 1). Initially, the lesions appeared on the chest and back,

coalescing into larger lesions, primarily on the chest and inner extremities (Fig. 2). The oral mucosa, palms, and soles were unaffected. The patient complained of pruritus and burning sensation in the affected areas.

The patient was then referred to a dermatologist. A comprehensive medical history was obtained and thorough physical examination was performed, after which antibiotics were immediately discontinued. Additionally, the skin lesions were treated with oil baths, moist dressings, antiseptic solutions, and topical corticosteroids.

A wide range of diagnostic procedures was performed. Laboratory tests, including complete blood count, differential blood count, liver enzymes, urea, and creatinine were normal; bacterial culture of pustular lesions, herpes simplex type 1 immunoglobulin G and M and Tzanck smear were negative. Furthermore, histopathologic analysis of a skin biopsy revealed the presence of a subcorneal spongiform pustule with a dense perivascular acute inflammatory infiltrate rich in neutrophils and eosinophils (Figs. 3 and 4). The dermis exhibited papillary edema with rare focal lymphocytes and plasma cells.



Fig. 1. Disseminated non-follicular pustules on an erythematous base.



Fig. 2. Coalescing lesions on the back.

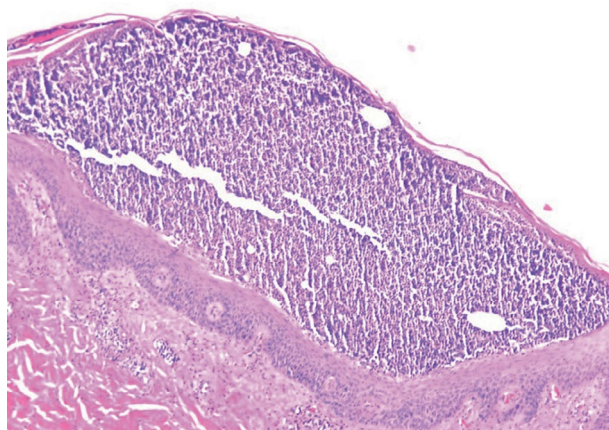


Fig. 3. Subcorneal pustule with a dense neutrophilic inflammatory infiltrate.

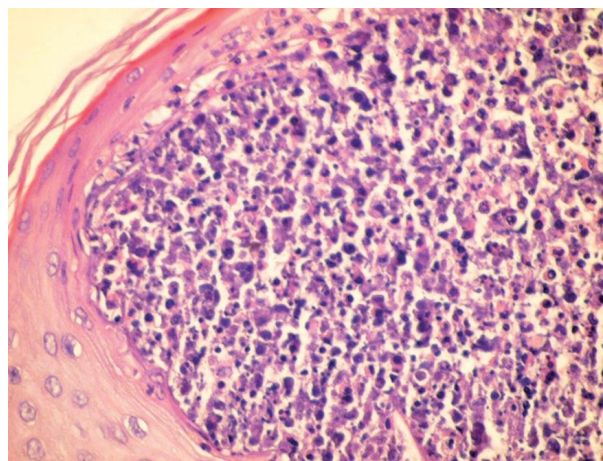


Fig. 4. Dense neutrophilic infiltrate.

The diagnosis of AGEP was made and confirmed based on the validation score developed by the EuroSCAR group. Following discontinuation of antibiotic treatment for seven days, the pustular lesions regressed,

however, erythema, pruritus, and residual desquamation persisted. After one month, all skin changes had completely resolved, and a patch test is planned to identify which drug caused AGEP.

Discussion

The clinical features of AGEP include numerous small, sterile, non-follicular pustules on an erythematous base, primarily located on the trunk and intertriginous regions. Mucous membrane involvement may or may not be present²⁻⁴. Immunologically, AGEP is considered a T cell-mediated neutrophilic inflammatory disease involving drug-specific CD4+ T cells, cytotoxic CD8+ T cells, T helper 17 (Th17) cells, and inflammatory cytokines and chemokines. Drug-specific CD4+ T cells play a crucial role in recruiting neutrophils in tissues by producing large amounts of chemokines that promote neutrophil chemotaxis (CXCL8) and GM-CSF, which reduces neutrophil apoptosis^{2,5,6}.

Although it is a rare condition, with a global incidence of 1-5 cases *per* million individuals *per* year, it is important to consider AGEP when diagnosing a patient with a drug-induced skin eruption. AGEP predominantly affects adults, mean age of 57.8 years^{2,3}.

In approximately 90% of cases, AGEP is caused by systemic exposure to drugs, most commonly aminopenicillins, quinolones, hydroxychloroquine, sulfonamides, terbinafine, diltiazem, ketoconazole, fluconazole, and macrolides^{2,3}. Isolated cases of AGEP have also been associated with intravenous contrast agents and viral, bacterial or parasitic infections (such as enterovirus, adenovirus, cytomegalovirus, parvovirus B19, *Mycoplasma pneumoniae*). However, the cause remains unidentified in up to 10% of cases^{3,7,8}.

The majority of AGEP cases are triggered by antibiotics, as antibiotics are among the most commonly prescribed drugs. Studies have shown that an outbreak typically occurs within a few hours to a few days after the administration of the causative drug. Studies specifically focusing on antibiotic-induced AGEP have reported a median time of one day between drug exposure and onset of symptoms⁸.

The diagnosis of AGEP relies on a validation assessment developed by the EuroSCAR group, which considers factors such as the morphology of skin lesions (presence of pustules, erythema, and typical distribution), clinical course (acute onset, high fever, blood neutrophilia, mucosal involvement, post-pustular desquamation, resolution within 15 days) and histologic findings (including exocytosis of polymorphonuclear

cells, subcorneal and/or intraepidermal pustules, papillary edema). Patients are categorized as having definitive, probable, possible, or no AGEP^{2,8}. A drug patch test can be used to determine the cause of AGEP when the responsible drug is unclear. The sensitivity of the patch test is uncertain but is generally estimated to be around 50%. While patch tests appear to be safe, mild recurrence of AGEP skin symptoms or other rashes may occur, primarily on the skin areas tested^{12,4,9,10}.

Acute generalized exanthematous pustulosis poses a diagnostic challenge due to numerous differential diagnoses, including generalized acute pustular psoriasis (von Zumbusch), subcorneal pustular dermatosis (Sneddon-Wilkinson disease), Stevens-Johnson syndrome/toxic epidermal necrolysis, intercellular IgA dermatosis-IgA pemphigus, and generalized pustulous necrotizing vasculitis²⁻⁴. Compared to other cutaneous adverse reactions, AGEP is associated with a lower morbidity. Systemic complications of AGEP include acute renal insufficiency and hepatitis, which occur in 20% of cases, with a mortality rate of less than 5%^{2,4,11}.

The primary treatment approach for AGEP involves discontinuation of the suspected drug, which results in improvement within several days, along with supportive measures such as the use of topical corticosteroids, moist compresses, and antiseptic solutions^{2,4}.

The case we presented is unique as our literature search did not identify similar cases involving the use of several different antibiotics within such a short period. Such cases highlight the importance of early identification of AGEP and prompt discontinuation of antibiotic treatment instead of switching to alternative antibiotics. It is important to emphasize that the uncontrolled use of antimicrobial agents can result in even more serious drug-related adverse reactions.

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Sažetak

AKUTNA GENERALIZIRANA EGZANTEMATOZNA PUSTULOZA (AGEP) UZROKOVANA ANTIBIOTSKOM POLITERAPIJOM: PRIKAZ SLUČAJA

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Akutna generalizirana egzantematozna pustuloza (AGEP) je rijetka bolest, uglavnom uzrokovana lijekom ili infekcijom. U kliničkoj slici prevladava nagli nastanak brojnih nefolikularnih pustula na eritematoznoj podlozi, uz prateće sistemske simptome. Histološka slika je obilježena supkornealnim, intraepidermalnim, spongiformnim pustulama, edemom papilarnog dermisa te vazodilatacijom krvnih žila u dermisu koje okružuju infiltrate neutrofila, eozinofila i mononuklearnih stanica. Cilj ovoga rada je prikazati dosadašnja saznanja o nastanku, liječenju, kliničkoj te histološkoj slici AGEP-a. Prikazan je slučaj 50-godišnjeg bolesnika kojem je prepisano više različitih vrsta antibiotika te koji je razvio kožni oblik reakcije na lijek. Osnova liječenja je brza identifikacija uzročnog lijeka, njegovo ukidanje iz terapije te ostale suportivne mjere, uz očekivano povlačenje simptoma unutar dva tjedna. Brzo postavljanje dijagnoze i pravodobno liječenje dovode do poboljšanja općeg stanja i sprječavaju razvoj sistemskih komplikacija.

Ključne riječi: Akutna generalizirana egzantematozna pustuloza; Reakcija na lijek; lijekovi; Antibiotici