Acute Generalized Exanthematous Pustulosis Complicated by Acute Tubular Necrosis: Case Report

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Abstract

Acute generalized exanthematous pustulosis (AGEP) is a severe cutaneous adverse reaction characterized by the rapid onset of non-follicular sterile pustules on an erythematous base. In most cases, it is associated with drug administration, with antibiotics being the most frequently implicated, although a wide range of medications can trigger this condition. Typically, within 48 hours after exposure to the causal drug, fever and pustular eruption accompanied by leukocytosis occur. We present the case of a 57-year-old man admitted to the hospital with a right foot ulcer, who after several days of treatment with meropenem and vancomycin developed a generalized skin rash with fever, leukocytosis with eosinophilia, and acute kidney injury. A skin biopsy confirmed the diagnosis of AGEP. The patient received treatment with methylprednisolone pulses, hydroxyzine, and topical mupirocin, which led to significant clinical improvement and allowed hospital discharge. This case highlights the importance of early recognition of severe antibiotic-induced cutaneous reactions and their potential association with

systemic complications such as acute tubular necrosis, underscoring the need for timely diagnostic and therapeutic interventions to reduce morbidity and mortality.

Keywords: Acute generalized exanthematous pustulosis; meropenem; vancomycin; severe cutaneous adverse reactions.

Introduction

Acute generalized exanthematous pustulosis (AGEP) is a rare neutrophilic dermatosis with sudden onset, characterized by the eruption of multiple small, sterile, non-follicular pustules on an erythematous and edematous base (1). The estimated incidence is approximately 1 to 5 cases per million inhabitants per year (2). It can occur in any age group, with a significant predominance in females (1).

AGEP is primarily associated with drug exposure in more than 90% of cases (3). The most commonly implicated medications include aminopenicillins, pristinamycin, sulfonamides, quinolones, hydroxychloroquine, terbinafine, and diltiazem. Additionally, in a small number of cases, it has been associated with bacterial, viral, and parasitic infections, such as parvovirus B19, ***Mycoplasma***, cytomegalovirus, coxsackie B4, ***Chlamydia pneumoniae***, ***Escherichia coli***, and ***Echinococcus*** (4).

Clinically, AGEP presents with cutaneous lesions characterized by multiple small, sterile, non-follicular pustules, associated with pruritus and a burning sensation. In some cases, these pustules may coalesce, clinically mimicking a positive Nikolsky sign (5). Mucosal involvement is observed in approximately 20% of cases, usually limited to a single site, such as the oral mucosa (6). Cutaneous symptoms are often accompanied by fever (≥38 °C) and neutrophilic leukocytosis, and occasionally mild eosinophilia (5). Systemic manifestations, including renal involvement, are uncommon (3).

Management consists of discontinuation of the identified causative agent and supportive care, which may include topical or systemic corticosteroids, antibiotic solutions during the pustular phase, and emollients during the desquamative phase (2).

We report the case of a 57-year-old male patient who developed AGEP following treatment with meropenem and vancomycin, who, in addition to the characteristic cutaneous manifestations, presented with acute tubular necrosis.

Case Presentation

A 57-year-old male patient, a farmer from the Cordillera department, with a relevant medical history of hypertension treated with telmisartan 80 mg/day and insulin-dependent diabetes mellitus managed with insulin degludec 28 IU before breakfast, with no history of drug allergies, presented to the emergency department with a two-month history of a dorsal right foot ulcer. The lesion was associated with purulent discharge, erythema, edema, and functional impairment.

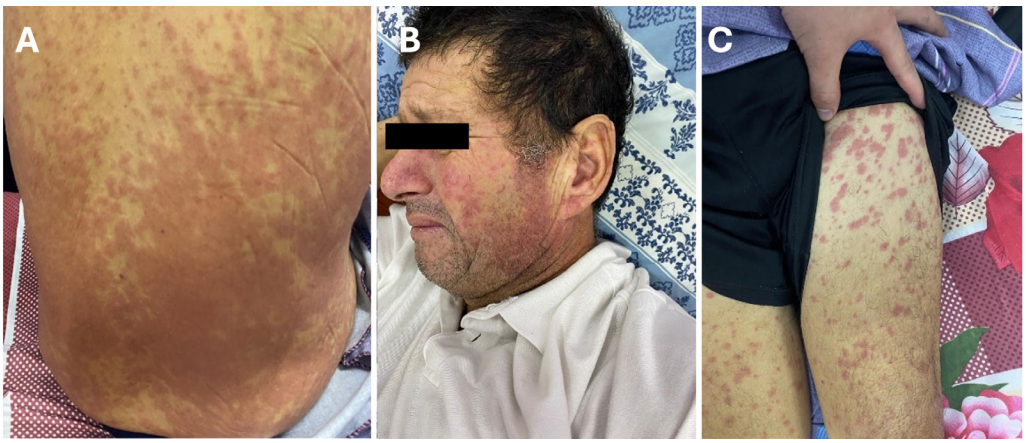
A diagnosis of Charcot neuroarthropathy was established, and a surgical fistulectomy was performed by the Orthopedics and Traumatology service. During the procedure, a microbiological culture sample was obtained, which was negative for bacterial growth. Subsequently, antibiotic therapy with clindamycin and ceftriaxone was initiated; however, no significant clinical improvement was observed, and purulent discharge persisted through the cutaneous fistula.

Due to the lack of response to initial treatment, a magnetic resonance imaging scan of the foot was requested, which confirmed the diagnosis of chronic osteomyelitis. Consequently, the antibiotic spectrum was broadened with a combination of meropenem and vancomycin.

After approximately 14 days of this treatment, the patient developed episodes of intermittent fever and a generalized erythematous rash accompanied by pustular lesions, predominantly on the anterior thoracic region. No hemodynamic compromise was observed, and no additional infectious focus was identified.

On physical examination, vital signs were stable, and an erythrodermic eruption was observed, predominantly affecting the anterior and posterior thorax, face, and thighs (Figure 1). No involvement of the mucosa, hair, or nails was noted.

Figure 1: Erythroderma predominantly involving the posterior thorax, face, and thighs. (A) Multiple non-follicular pustules with clear content are observed on the posterior thorax, most of them confluent. (B) Pustules on the face over an erythematous base. (C) Pustule on the thighs.

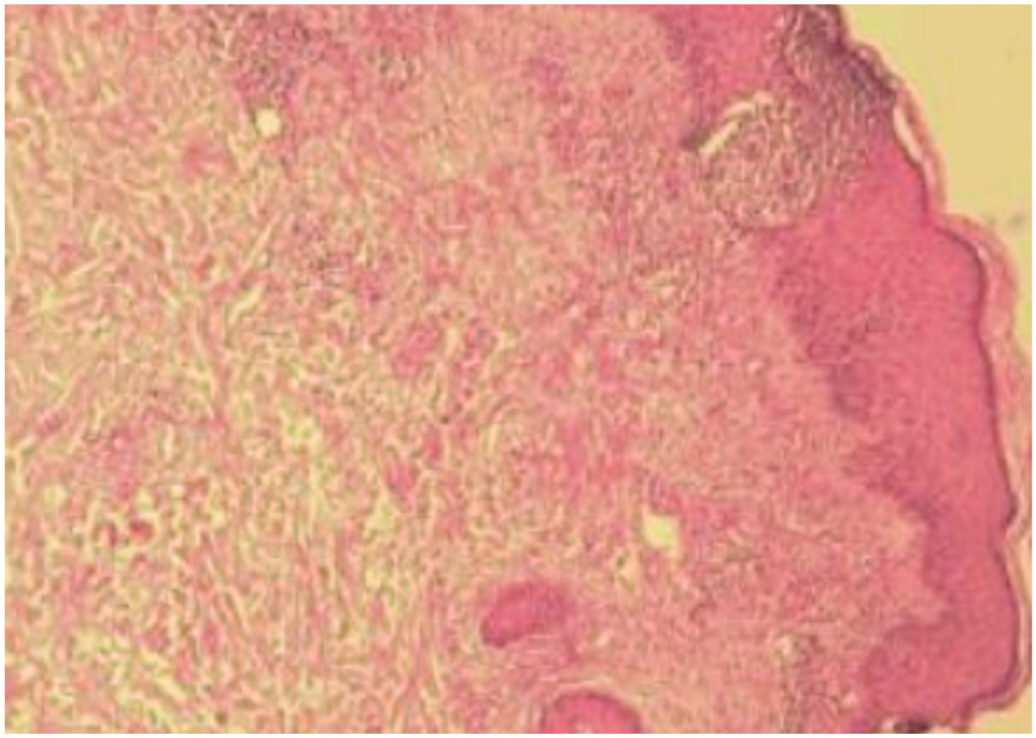


Simultaneously, laboratory tests revealed leukocytosis with significant eosinophilia (25%) and acute renal impairment, with creatinine levels reaching up to 5.2 mg/dL, decreased urine output to 0.2 mL/kg/h, reduced urine osmolality, eosinophiluria, granular casts, and tubular epithelial cells in the urinary sediment. Given the suspicion of an adverse drug reaction, antibiotic therapy was discontinued. Blood and urine cultures were obtained to rule out other infectious causes, and supportive measures for acute kidney injury were initiated.

Subsequently, skin biopsies were obtained, and treatment with methylprednisolone pulses (1000 mg/day for 5 days), antiparasitic therapy, and supportive measures such as antihistamines and topical treatment was initiated.

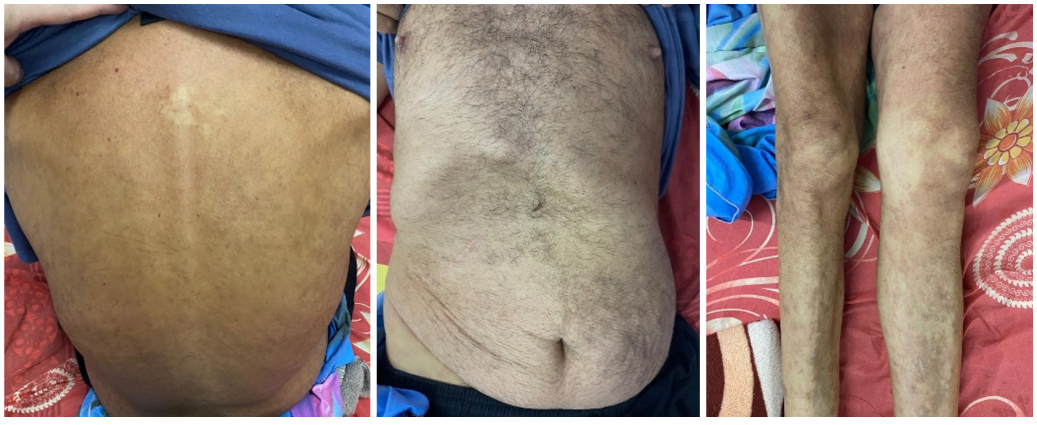
Histopathological analysis of the skin biopsy revealed subcorneal and intraepidermal neutrophilic pustules, papillary dermal edema, and a perivascular inflammatory infiltrate composed of neutrophils and a few eosinophils, confirming the diagnosis of AGEP (Figure 2).

Figure 2: Subcorneal and intraepidermal collections of neutrophils forming superficial microabscesses. Dermis showing a perivascular inflammatory infiltrate composed of lymphocytes and eosinophils (40×; H&E stain).



The patient continued treatment with oral prednisone at a dose of 40 mg/day for four days, followed by a gradual taper, along with hydroxyzine and topical mupirocin application. A marked clinical improvement was observed (Figure 3), as well as improvement in laboratory parameters, allowing hospital discharge after twenty days of treatment.

Figure 3: Clinical improvement with resolution of lesions following discontinuation of the suspected drugs and after initiation of the prescribed treatment.



Discussion

Acute generalized exanthematous pustulosis (AGEP) is part of a group of severe cutaneous adverse reactions. Approximately 90% of cases are drug-induced, particularly by antibiotics such as aminopenicillins, beta-lactams, and others (8). Cases associated with infectious agents, exposure to toxic substances such as mercury and heavy metals, chemotherapy, combined radiation therapy, and insect bites have also been reported (9). In the present case, the condition was most likely triggered by the administered antibiotics, possibly meropenem or vancomycin. However, due to prior exposure to other antibiotics, the specific causative agent cannot be definitively established.

AGEP is estimated to affect between 1 and 5 individuals per million per year (9). This condition is more common in women, with a mean age of approximately 56 years (10). An association between AGEP and higher body mass index (BMI) has also been described, potentially related to the upregulation of proinflammatory cytokines secondary to obesity (11). In the present case, the patient is male, with an age consistent with the average reported in the literature. However, his BMI was 22, which falls within the normal range according to the World Health Organization (WHO), differing from the reported association between AGEP and higher BMI.

According to the literature, the time to onset of drug-induced AGEP follows a bimodal distribution (12). For meropenem, the reported latency period is approximately 5 to 15 days after exposure (13), whereas for vancomycin it is shorter, ranging from 1.5 to 5 days (14). This suggests that different drugs may present distinct latency periods before triggering AGEP. In this case, the latency period was 14 days after initiation of antibiotic therapy with meropenem and vancomycin administered simultaneously. This timeframe falls within the reported range for meropenem, suggesting that this drug may be associated with the observed cutaneous adverse reaction.

Initial symptoms typically include high fever and generalized malaise, accompanied by leukocytosis—particularly neutrophilia—and eosinophilia in approximately 30% of patients. This is followed by the development of edematous erythema and a pruritic pustular eruption, mainly affecting the trunk and intertriginous areas, usually without mucosal involvement (5). The pustules are sterile, non-follicular, and typically numerous. In some cases, mucosal involvement may occur, although this is uncommon and generally limited to a single site (9). In the reported case, clinical manifestations were

consistent with those described in the literature, including fever, leukocytosis with eosinophilia, and a generalized pustular eruption without significant mucosal involvement.

Systemic involvement in AGEP is considered when organ dysfunction occurs alongside typical cutaneous findings and cannot be attributed to another cause or underlying disease (5). Studies indicate that approximately 17% to 20% of AGEP cases present with internal organ involvement, most commonly affecting the liver, kidneys, and lungs (15). In this case, significant renal involvement was observed, evidenced by markedly elevated serum creatinine levels, along with eosinophiluria and other markers of acute tubular necrosis, such as granular casts and renal tubular epithelial cells in the urinary sediment, suggesting acute kidney injury associated with AGEP.

The diagnosis of AGEP is based on a combination of clinical criteria and histological findings. The EuroSCAR group developed a scoring system that evaluates lesion morphology, clinical course, and histopathological findings to determine the likelihood of AGEP (17). This tool classifies patients into four categories: definite, probable, possible, or no AGEP. In this case, a total score of 10 points was obtained, classifying it as definite AGEP and confirming the diagnosis.

Histologically, AGEP is characterized by the presence of pustules in different layers of the epidermis, including intracorneal, subcorneal, and/or intraepidermal locations. Additionally, papillary dermal edema and an inflammatory infiltrate composed of neutrophils and eosinophils surrounding blood vessels and distributed interstitially within the dermis are observed (5). These findings are consistent with those observed in this patient, supporting diagnostic accuracy.

The differential diagnosis should include pustular psoriasis, DRESS syndrome (drug reaction with eosinophilia and systemic symptoms), toxic epidermal necrolysis (TEN), IgA pemphigus, Sneddon–Wilkinson syndrome, pemphigus herpetiformis, pustular Sweet syndrome, and pustular vasculitis (18).

Therapeutic management consisted of the immediate discontinuation of the suspected antibiotics, meropenem and vancomycin, followed by intravenous chlorphenamine for symptom control and methylprednisolone pulses to reduce inflammation. Subsequently, a tapering regimen of prednisone was initiated, consistent with recommendations reported in the medical literature for the management of this condition (5).

The prognosis is generally favorable, with resolution typically occurring within two weeks; however, severe cases may occur, particularly in elderly patients. The mortality rate is approximately 2% (19).

This case is noteworthy due to the rarity of AGEP, an uncommon dermatological condition. In this patient, the disease presented with typical and extensive cutaneous lesions accompanied by significant systemic involvement. Moreover, the associated renal impairment represents an uncommon complication in this context. Despite the severity of the clinical presentation, the patient showed a favorable response to the instituted treatment, highlighting the importance of timely and appropriate therapeutic management.

Conclusions

Acute generalized exanthematous pustulosis (AGEP) is a rare but potentially severe adverse cutaneous reaction, and its early recognition is essential to prevent systemic complications.

In the present case, the association with broad-spectrum antibiotics (meropenem and vancomycin) and progression to acute tubular necrosis highlight several key points:

- Early recognition: The appearance of a generalized pustular eruption in patients receiving antibiotic therapy should raise suspicion for AGEP.
- Immediate discontinuation of the suspected drug: This is the most important therapeutic measure to halt disease progression.
- Systemic evaluation: Although uncommon, renal involvement may occur and requires a comprehensive approach with timely clinical support.
- Importance of skin biopsy: Histopathological confirmation is essential to differentiate AGEP from other pustular dermatoses and to guide appropriate management.
- Appropriate treatment: The use of systemic corticosteroids and supportive measures allowed clinical resolution and functional recovery in this patient.

This case emphasizes the need for a broad and multidisciplinary diagnostic approach in severe cutaneous adverse reactions, as well as the importance of considering uncommon systemic complications, such as acute tubular necrosis, in the context of AGEP.

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