Acute Generalized Exanthematous Pustulosis As A Cause of Exfoliative Dermatitis: A Case Report

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Abstract

Introduction: Acute generalized exanthematous pustulosis (AGEP) is a rare cutaneous adverse drug reaction characterized by an acute sterile pustular eruption and may present as erythroderma with extensive desquamation.
Case Presentation: A 59-year-old man presented with generalized erythema, pustules, fever, and extensive desquamation after exposure to multiple medications. Examination revealed diffuse erythematous plaques, scaling, erosions, and confluent pustules. Laboratory evaluation showed leukocytosis and elevated C-reactive protein. Histopathology demonstrated subcorneal pustules with neutrophilic and lymphocytic infiltrates, with negative microbiological investigations. A EuroSCAR score of 10 confirmed definite AGEP. The patient improved markedly within 9 days after withdrawal of suspected drugs, systemic corticosteroids, and supportive treatment, allowing discharge with good skin condition.
Discussion: AGEP is an important cause of acute erythroderma and may be triggered by medications such as amoxicillin and analgesics. Recurrence may occur following re-exposure.
Conclusion: AGEP should be considered in patients with acute erythroderma and pustules following recent drug exposure.

Keywords: Acute generalized exanthematous pustulosis (AGEP), exfoliative dermatitis (erythroderma), drug eruption, sterile pustules.

Introduction

Acute generalized exanthematous pustulosis (AGEP) is a rare, acute cutaneous adverse drug reaction characterized by the rapid eruption of numerous small, sterile, non-follicular pustules on an erythematous and often edematous base. The entity evolved from the clinical spectrum of generalized pustular psoriasis. In 1968, Baker and Ryan described a subgroup of patients with acute pustular eruptions without a previous history of psoriasis, which they classified as the exanthematic type. In 1980, Beylot et al. introduced the term pustulose exanthématique aiguë généralisée (PEAG), subsequently translated as acute generalized exanthematous pustulosis (AGEP). [1,2]

AGEP is predominantly drug-induced and typically develops rapidly after exposure to the culprit medication. It is most commonly associated with β-lactam, macrolide and quinolone, antibiotics, anticonvulsants, sulfonamides, calcium channel blockers (diltiazem), and terbinafine. The estimated incidence of AGEP is approximately 1 to 5 cases per million per year. Clinically, AGEP is characterized by widespread pinhead-sized, non-follicular sterile pustules, often beginning in intertriginous areas or the face and rapidly spreading to the trunk and extremities. Fever and neutrophilic leucocytosis are common, whereas mucosal involvement is generally mild and occurs in a minority of patients. The eruption usually resolves rapidly following withdrawal of the causative drug, with superficial desquamation during the resolution phase. [3,4]

Extensive desquamation may produce a clinical picture of generalized erythema and scaling resembling exfoliative dermatitis (erythroderma). Exfoliative dermatitis is a reaction pattern rather than a specific disease and may result from drug reactions, inflammatory dermatoses, malignancy, or other systemic conditions. Because AGEP may clinically overlap with generalized pustular psoriasis and infectious pustular disorders, recognition of its characteristic morphology, temporal relationship with drug exposure, and histopathological features is essential. Discontinuance of therapy is usually the extent of treatment necessary in most patients, although some patients may require the use of corticosteroids. [3,4]

Herein, we report a case of exfoliative dermatitis secondary to AGEP following exposure to multiple potential culprit medications. The extensive desquamative presentation highlights the importance of considering AGEP in the cause of acute exfoliative dermatitis.

Case Presentation

A 59-year-old man presented to our hospital with a chief complaint of generalized skin peeling. Two days before admission, he developed widespread erythematous lesions followed by extensive desquamation involving almost the entire body. The eruption was associated with pruritus and a burning sensation and was accompanied by fever. The patient denied painful lesions or involvement of the oral, ocular, or genital mucosa, as well as arthralgia. No nail abnormalities were reported. Approximately two weeks before admission, the patient had initially developed erythematous lesions on the buttocks, chest, back, arms, and legs. These lesions were associated with pruritus, a burning sensation, and pustular lesions containing purulent material. The patient had been exposed to several medications, including an herbal preparation, an analgesic and amoxicillin prescribed for toothache. Two days after taking these medications, he developed a new generalized eruption characterized by erythematous lesions followed by widespread skin peeling.

The patient had a history of a similar episode approximately one year earlier, when he was hospitalized at our institution and diagnosed with erythroderma secondary to a suspected drug eruption, with ciprofloxacin considered the suspected culprit. He also had a history of type 2 diabetes mellitus, for which he was not taking medication regularly, and was an active smoker. No other significant medical history was reported.

On admission, his vital signs were within normal limits, and his body mass index was 30.5 kg/m². Dermatological examination revealed multiple discrete erythematous macules and plaques with diffuse, poorly defined borders involving the anterior and posterior thorax and bilateral upper and lower extremities. The lesions were accompanied by thin superficial scales and areas of erosion. On the scalp, erythematous macules with ill-defined borders and thick yellowish scales were observed. Multiple confluent areas of pustules were present in the crural region (Figure 1).

Figure 1. Dermatological status of 1st visit.

Laboratory investigations revealed leukocytosis, hypoalbuminemia, and an elevated C-reactive protein level. Potassium hydroxide examination and Gram staining did not demonstrate fungal or bacterial organisms, and blood cultures showed no bacterial growth or sterile. Radiological examination revealed no significant abnormalities. Skin biopsy demonstrated subcorneal pustule formation accompanied by acanthosis and mild spongiosis. The superficial dermis showed dense inflammatory infiltrates predominantly composed of lymphocytes and neutrophils, together with dilated capillary blood vessels (Figure 2). These histopathological findings were compatible with AGEP.

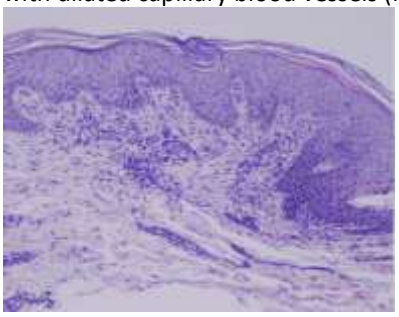

Figure 2. Histopathological examination

The diagnosis of AGEP was further supported by a EuroSCAR validation score of 10, corresponding to a definite diagnosis of AGEP. The combination of an acute pustular eruption, recent exposure to multiple medications, fever, leukocytosis, absence of significant mucosal involvement, and characteristic histopathological findings supported AGEP as the underlying cause of the patient's exfoliative dermatitis. Based on the clinical, laboratory, and histopathological findings, the patient was diagnosed with exfoliative dermatitis secondary to AGEP. Because the patient had been exposed to multiple potential culprit drugs, including amoxicillin, analgesics, herbal medicine, and other unidentified medications, the specific causative drug could not be definitively determined. All suspected culprit medications were discontinued.

The patient was treated with intravenous dexamethasone 5 mg three times daily (15 mg/day), corresponding to approximately 1.28 mg/kg/day of prednisone equivalent, followed by gradual tapering according to the clinical response. Cetirizine 10 mg once daily at night was administered for symptomatic relief of pruritus. Topical therapy included desoximetasone 0.25% cream twice daily for erythematous lesions on the trunk and extremities and mometasone furoate cream twice daily for facial lesions. Sodium fusidate cream was applied twice daily to erosive areas, while Levertrans topical preparation was applied twice daily to areas with thick scales. A pseudoceramide moisturizer cream was applied twice daily to the face and body for skin barrier support. Frequent compresses with 0.9% sodium chloride solution were applied to the scalp to facilitate removal of thick scales. The patient was managed collaboratively with the Internal Medicine Department, particularly in view of his history of type 2 diabetes mellitus. Following withdrawal of the suspected culprit medications and initiation of treatment, the patient showed progressive clinical improvement. No new pustular or erythematous lesions developed during hospitalization, and the fever gradually subsided. By day 4 of treatment, the erythema and scaling had substantially decreased, allowing dexamethasone to be tapered to 7.5 mg/day. Further clinical improvement was observed by day 7, with continued reduction in erythema and scaling and no emergence of new lesions. Dexamethasone was subsequently tapered to 5 mg before being discontinued. By day 9, the patient's skin lesions had markedly improved, with substantial resolution of erythema and desquamation and no new pustular lesions (Figure 3). He was discharged in stable condition with a continued steroid-tapering regimen and scheduled for follow-up at the Dermatology and Venereology outpatient clinic.

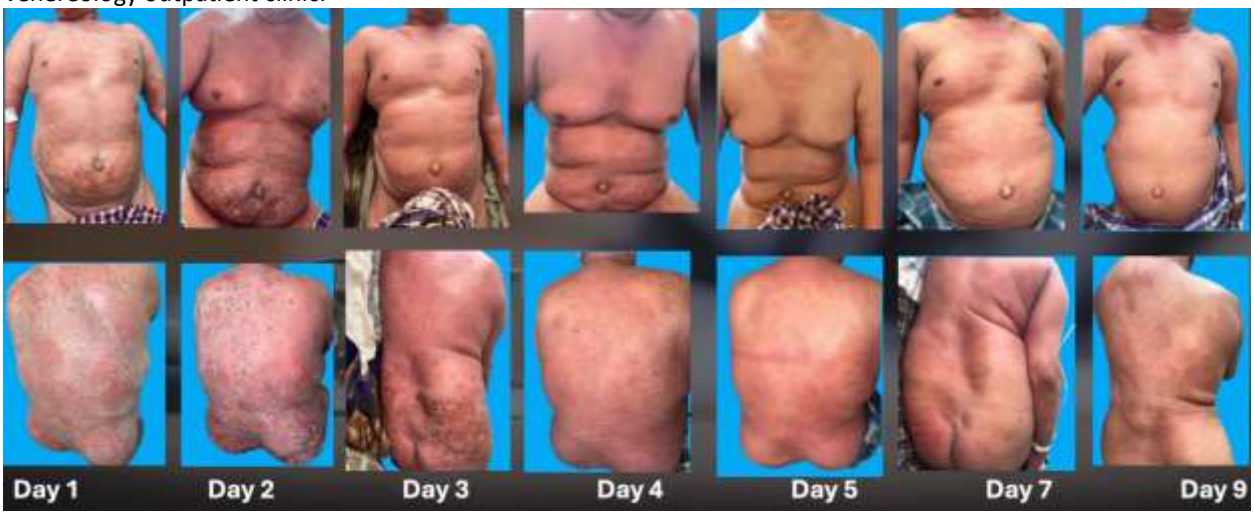

Figure 3. Progress of the lesion

Discussion

AGEP is an acute febrile pustular eruption that occurs 24 to 48 hours after initiation of the implicated drug. It is characterized by small monomorphous nonfollicular sterile pustules concentrated on the trunk and intertriginous regions. Systemic features include leukocytosis with neutrophilia, fever, elevated liver enzymes with steatosis or hepatomegaly, renal insufficiency, and pleural effusions with hypoxemia. Generalized desquamation occurs after approximately 2 weeks.

Although AGEP is predominantly drug-induced, other triggers, including infections, vaccines, and non-drug substances, have also been reported. Antibiotics, particularly β-lactams such as amoxicillin, are among the frequently implicated drugs. The pathogenesis involves a drug-specific T-cell-mediated hypersensitivity reaction with

contributions from both adaptive and innate immune mechanisms. Drug-specific CD4+ and CD8+ T cells contribute to keratinocyte injury and cytokine production, while IL-8/CXCL8, IL-17, IL-36, granulocyte-macrophage colony-stimulating factor, and tumor necrosis factor-α promote neutrophil recruitment and activation, resulting in the characteristic sterile pustules. [4-6]

The present case is notable because the clinical manifestation progressed beyond the typical pustular eruption to extensive desquamation and exfoliative dermatitis. Exfoliative dermatitis, or erythroderma, is a clinical reaction pattern characterized by generalized erythema and scaling involving more than 90% of the body surface area. It may result from various underlying disorders, including psoriasis, eczematous dermatoses, drug reactions, and cutaneous T-cell lymphoma. Drug reactions are particularly important causes of acute erythroderma and should be carefully considered when there is a recent history of medication exposure. [7,8]

In this patient, the extensive erythema, scaling, erosion, and subsequent generalized desquamation resulted in a clinical picture of exfoliative dermatitis. However, the presence of pustules, particularly the confluent pustular lesions in the crural region, provided an important diagnostic clue toward AGEP. The typical evolution of AGEP begins with an acute erythematous eruption, frequently involving the face or intertriginous areas, followed by numerous small non-follicular pustules. Pruritus and burning sensations are common, while fever and neutrophilic leukocytosis frequently accompany the cutaneous eruption. Subsequent superficial desquamation is characteristic and usually occurs during the resolution phase. Mucosal involvement is generally absent or mild and occurs in less than 20% of patients. [3,9]

The temporal relationship between drug exposure and eruption in this case also supported AGEP. More than 90% of AGEP cases are associated with medications, with β-lactam antibiotics among the most frequently implicated drug classes. Amoxicillin is particularly relevant because aminopenicillins were among the drugs most strongly associated with AGEP in the multinational EuroSCAR case-control study. A recent multicentre study also identified antibiotics, particularly amoxicillin, as frequent triggers. [10,11] In the present case, however, identification of a single culprit drug was challenging because the patient had been exposed to several potential triggers, including an herbal preparation, an analgesic, and amoxicillin. Furthermore, the patient had previously experienced a similar eruption approximately one year earlier following exposure to ciprofloxacin. Therefore, although amoxicillin represents a biologically plausible culprit, the available clinical information does not permit definitive attribution to a single medication. [12] Obesity has been reported in association with AGEP in some clinical series; however, the available evidence is insufficient to establish obesity as an independent risk factor or causal contributor to AGEP. Therefore, in this patient, obesity should be regarded as a relevant clinical characteristic rather than a confirmed contributor to the pathogenesis of AGEP. [9]

The differential diagnosis includes pustular psoriasis, bacterial folliculitis or other infectious pustular disorders, drug-induced erythroderma, DRESS, HSR with pustulation, subcorneal pustular dermatosis (Sneddon-Wilkinson disease), pustular vasculitis and Stevens–Johnson syndrome/toxic epidermal necrolysis (SJS/TEN). Pustular psoriasis may clinically resemble AGEP but generally has a different clinical context and may be associated with a personal or family history of psoriasis. In contrast, the rapid onset, sterile non-follicular pustules, prominent neutrophilia, recent drug exposure, and rapid improvement after withdrawal of the suspected medications favored AGEP in this patient. Bacterial infection was also considered; however, Gram staining and cultures did not demonstrate bacterial infection. The absence of significant mucosal involvement and the lack of epidermal necrosis or blistering argued against SJS/TEN. [3,4,9]

Histopathology further supported the diagnosis. Characteristic histological features of AGEP include spongiform subcorneal and/or intraepidermal pustules, an often marked edema of the papillary dermis, and perivascular infiltrates with neutrophils and exocytosis of some eosinophils that consistent in this case. [4,9,13] The diagnosis was further strengthened by a EuroSCAR score of 10, corresponding to a definite diagnosis of AGEP. The EuroSCAR algorithm integrates the morphology and distribution of pustules, clinical course, associated features, histopathology, and exclusion of alternative diagnoses. In this case, the high score was particularly useful because the extensive desquamation and exfoliative phenotype could initially suggest other causes of erythroderma. [14]

Management of AGEP primarily consists of prompt withdrawal of the suspected causative drug and supportive care. Current European expert consensus emphasizes discontinuation of the suspected culprit, assessment for systemic involvement, and appropriate topical anti-inflammatory treatment. Topical corticosteroids are recommended for cutaneous inflammation, while systemic corticosteroids may be considered in very severe cases, particularly when erythroderma and disseminated pustules are present. Importantly, the evidence supporting systemic corticosteroids remains limited, and they are not considered mandatory for all patients with AGEP. [3] In this patient, the extensive

exfoliative dermatitis and disseminated pustular eruption justified hospitalization and intensive supportive management.

Treatment consisted of withdrawal of all suspected culprit medications, systemic dexamethasone, topical corticosteroids, antihistamine therapy, emollient therapy, treatment of erosive areas, and wet compresses for the thick scalp scales. This approach addressed both the underlying AGEP and the consequences of extensive exfoliative dermatitis, particularly disruption of the skin barrier. [3,8] The use of systemic corticosteroids in this case warrants consideration. The 2024 European expert consensus suggests that in very severe AGEP, including cases with erythroderma and disseminated pustules, a short course of systemic corticosteroids equivalent to prednisone 0.5 mg/kg/day for approximately 5–7 days may be considered. Therefore, the initial corticosteroid dose used in this patient was relatively intensive compared with the current consensus recommendation, but was selected in the context of extensive exfoliative dermatitis and disseminated pustulation. [3] Despite the limited evidence for systemic corticosteroids, observational data provide some support for their use in severe disease. In a retrospective study of 43 patients with AGEP from an Asian academic medical center, 9 patients (21%) received systemic corticosteroids, and systemic corticosteroid treatment was associated with a shorter median hospital stay compared with patients who did not receive systemic corticosteroids (6 vs. 10 days, p=0.035). However, the retrospective design and potential differences in baseline characteristics preclude establishing a causal treatment effect. [15]

The patient's clinical response was favorable. The rapid improvement is consistent with the generally self-limited nature of AGEP after removal of the causative trigger. AGEP commonly resolves within approximately 15 days, although the duration may vary according to disease severity and systemic involvement. [3,9] The rapid resolution in this patient is particularly relevant because erythroderma can result in substantial physiological disturbance through impaired skin-barrier function, increased transepidermal water loss, fluid and electrolyte abnormalities, thermoregulatory dysfunction, and increased metabolic demands. Consequently, hospitalization may be warranted for patients with extensive erythroderma to facilitate evaluation of the underlying cause and monitoring for systemic complications. In this case, supportive skin care with emollients and wet compresses, together with systemic management and multidisciplinary care, supported recovery during the acute phase. [7,8]

AGEP may recur following re-exposure to the responsible medication, making accurate identification and documentation of suspected culprit drugs important for future drug avoidance. Because this patient had multiple possible drug exposures and no definitive culprit was established, formal allergological evaluation after complete clinical recovery may be useful to clarify drug causality and identify safe alternatives. Patch testing can be considered after the acute episode, although its sensitivity is imperfect. Current European recommendations suggest follow-up approximately one month after discharge to assess complete healing and organize an appropriate allergological work-up. [3,12]

Conclusion

Overall, this case demonstrates an unusual clinical spectrum of AGEP in which the extensive desquamative phase manifested as exfoliative dermatitis. The combination of acute pustular eruption, recent medication exposure, systemic inflammatory findings, characteristic histopathology, negative microbiological evaluation, and a EuroSCAR score of 10 enabled the diagnosis of exfoliative dermatitis secondary to AGEP. Early recognition and prompt withdrawal of suspected culprit medications, together with appropriate supportive and anti-inflammatory treatment, were followed by substantial clinical improvement within nine days. [3,9]

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