SKIN

BRIEF ARTICLE

A Unique Presentation and Unusual Cause of Acute Generalized Exanthematous Pustulosis: A Case Report

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ABSTRACT

Acute generalized exanthematous pustulosis (AGEP) is a febrile, pustular eruption that has been reported in all ages. Three weeks following oral terbinafine use, a 64-year-old male patient was admitted to the hospital for diffuse, nearly confluent erythematous plaques and desquamation, fevers, chills, and ulcer formation on his lower mucosal lip and tongue. Ten days prior to presentation, he was evaluated and discharged with a prednisone 60 mg taper for suspected erythema multiforme. Terbinafine was discontinued and the patient was monitored for systemic involvement. Recognition of subtle pustules on a background of EM-like lesions may facilitate the timely diagnosis and appropriate treatment of AGEP.

INTRODUCTION

Acute generalized exanthematous pustulosis (AGEP) is a severe, acute-onset cutaneous eruption of small, sterile pustules on an erythematous base, occurring with fever and a neutrophilic leukocytosis.[1,2] AGEP primarily presents as an adverse drug reaction beginning 2-14 days following drug ingestion. The condition resolves spontaneously with desquamation within 1-2 weeks of drug discontinuation. Here, we describe an unusual presentation of AGEP and discuss disease pathophysiology, histopathology, and current treatment guidelines.

CASE REPORT

A 64-year-old male was admitted to the hospital for a painful rash that began three weeks after starting oral terbinafine for onychomycosis. The rash began on his neck and spread caudally to involve the trunk and extremities. The patient also had fevers, chills, and ulcer formation on his lower mucosal lip and tongue. Ten days prior to presentation, he was evaluated at an outside hospital and discharged with a prednisone 60 mg taper for suspected erythema multiforme. A biopsy was not performed at this time. However, his rash continued to worsen after starting prednisone.

On physical examination, he had diffuse, nearly confluent erythematous plaques with desquamation on the back, chest, and abdomen (**Figure 1**). There were erythematous patches with dusky centers on the thighs, legs, arms, hands, and palms (**Figure 2**). Several small clusters of grouped pustules were present on the calves and thighs (**Figure 3**). Few erosions were noted in the lower mucosal lip and right tongue. Nikolsky sign was negative, and there was no

ocular involvement or lymphadenopathy. Pertinent positive laboratory findings included WBC 19.5 (4.5-10 thou/cmm), absolute neutrophils 16.8 (1.8-7.8 thou/cmm), absolute monocytes 1.4 (0.3-1.0 thou/cmm), and CRP 93 (<7mg/L). Comprehensive metabolic panel and sedimentation rate were within normal limits. A skin biopsy from the left thigh revealed spongiotic dermatitis with eosinophils. Given clinical findings and the late timing of the skin biopsy, the diagnosis of AGEP was favored.

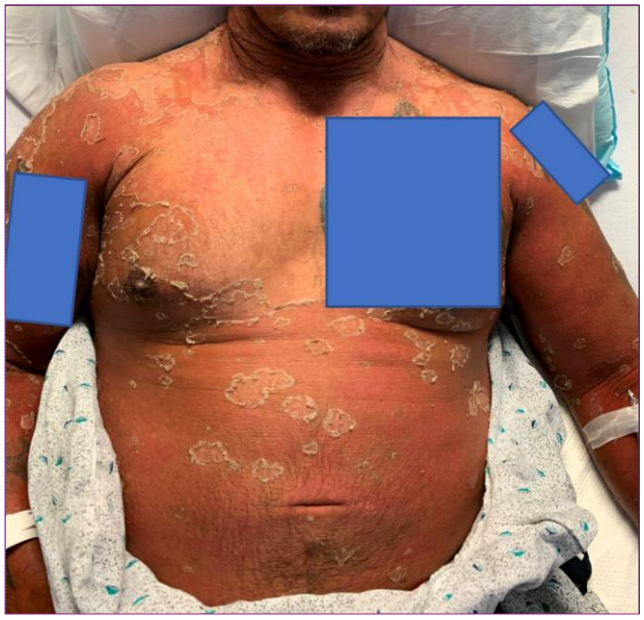

Figure 1. Confluent erythematous plaques with desquamation on the torso.

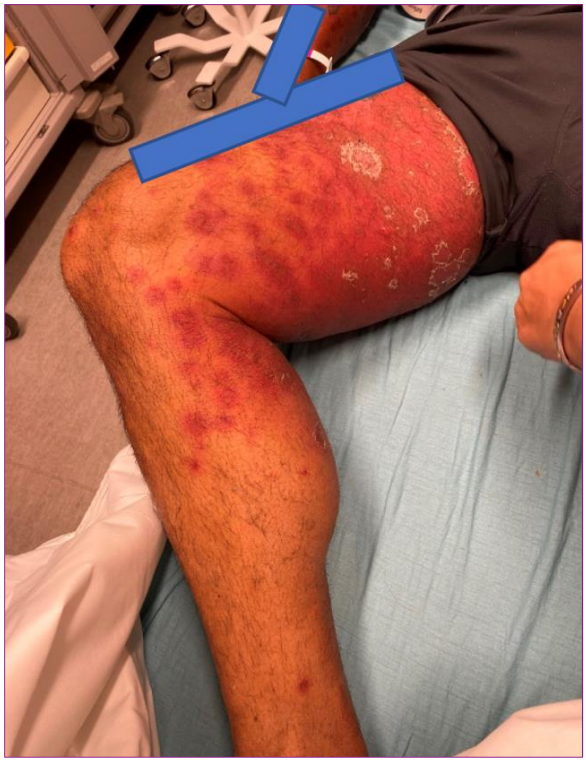

Figure 2. Erythematous patches with dusky centers on the right lower extremity.

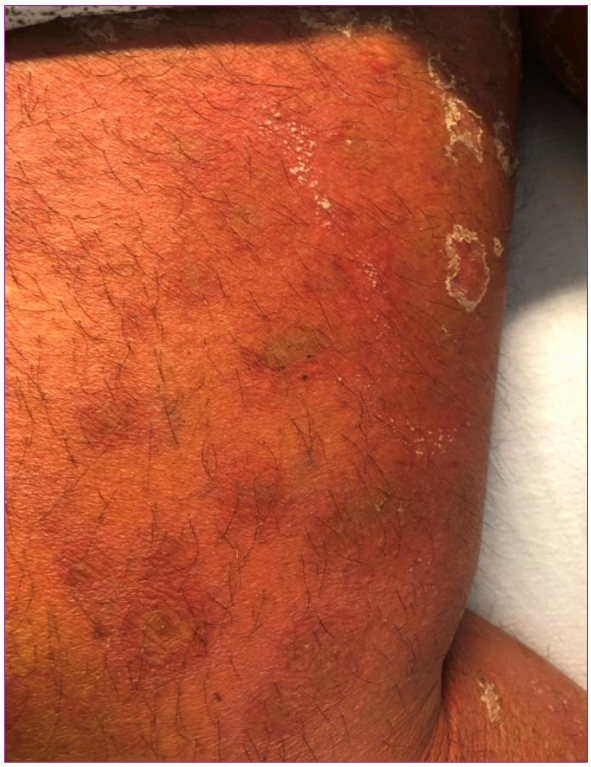

Figure 3. Small clusters of pustules on the thigh

DISCUSSION

Acute generalized exanthematous pustulosis (AGEP) is a febrile, pustular eruption that has been reported in all ages. In the adult population, 90% of cases are a result of an adverse medication reaction, while viral infections are the most common cause in pediatric cases.

Antibiotics, particularly aminopenicillins, cephalosporins, quinolones, and sulfonamides are among the most cited offending agents.[2] Other medications have been implicated including calcium channel blockers, carbamazepine, antimalarials, fluconazole, and ibuprofen.[3] Rarely, reports have associated AGEP with terbinafine use, as in our patient's presentation. Onset of the drug eruption may appear anywhere between two days to two weeks following ingestion of the inciting agent. In our patient's unique case, he had a delayed onset of this cutaneous eruption three weeks after terbinafine ingestion. Following complete resolution of AGEP, patch testing can be used to determine the offending agent if it is unclear. Infectious agents, including parvovirus B19, cytomegalovirus, chlamydia pneumoniae, mycoplasma pneumoniae, coxsackie B4, Escherichia coli, and echinococcus have been implicated, especially in the pediatric population.[2,4] Rare cases have been reported with the bite of the brown recluse spider, mercury, and iopamidel, a radiocontrast media. [5,6]

AGEP is characterized by acute onset of multiple, superficial, tiny (<5 mm) pustules on erythematous plaques classically beginning on the face and intertriginous areas and spreading cephalocaudally. The eruption may be associated with burning, pruritus, and facial edema. While unlikely, mucosal involvement has been reported and is generally limited to one mucosal region, often the lips or buccal mucosa.[2,4] The rash resolves within several weeks with collarette-shaped or pinpoint foci of desquamation.[2]

Manifestations of AGEP may mimic erythema multiforme (EM), presenting with targetoid lesions, with or without mucosal involvement. In such presentations, pustules may be a late presenting sign of AGEP, as seen in our case. Recognition of subtle pustules on a background of EM-like lesions may facilitate the timely diagnosis of AGEP and alter the treatment course. AGEP is often drug-induced whereas erythema multiforme is often caused by an infectious etiology, most commonly herpes simplex virus. In our patient's case, a presumed diagnosis of erythema multiforme may have prompted empiric treatment with antiviral therapy, as well as allowed for possible re-initiation of terbinafine in the future, which could have caused relapse of his cutaneous eruption. Additionally, EM does not typically require specific laboratory monitoring whereas patients with AGEP must be monitored for liver and kidney dysfunction.[7] Other atypical presentations of AGEP may mimic the morbilliform rash of drug reaction with eosinophilia and systemic symptoms (DRESS) or the blisters and desquamation of toxic epidermal necrolysis (TEN).

The pathophysiology of AGEP involves a type-IV hypersensitivity reaction as demonstrated by in vitro and patch testing. In the early stage, drug-specific CD4 T-cells proliferate and migrate to the epidermis, inducing apoptosis of keratinocytes and leading to vesicle formation.[4] Release of interleukin (IL)-8 results in neutrophilic chemotaxis, while secretion of interferon-gamma and macrophage colony stimulating factor (MCSF) aids in neutrophilic survivability.[4] Coupled together, this results

in the transformation of vesicles into sterile pustules.

Recent research suggests an increased predisposition to AGEP in patients with IL36RN gene mutations. The IL36RN gene encodes for the anti-inflammatory interleukin, IL-36Ra, which functions to block the pro-inflammatory IL-36.[8] When mutated, there is uninhibited IL-36 signaling and increased downstream production of IL-8, thus facilitating pustule formation.[8]

Histopathology can be diagnostic, demonstrating intraepidermal, intracorneal, and subcorneal pustules that mainly contain a neutrophilic, possibly eosinophilic, infiltrate.[4] Epidermal spongiosis and papillary dermal edema with a mixed infiltrate may also be present.[2,4]

Treatment includes withdrawing the causative medication and monitoring for systemic involvement. The rash will self-resolve over the course of 1-2 weeks. Topical steroids and antihistamines may be utilized to relieve associated pruritis. In severe cases, systemic prednisone or oral cyclosporine may be indicated, however there is no evidence that these therapies shorten disease duration.[1,2] Mortality from AGEP is rare (<5%) and occurs in patients with comorbidities presenting with mucosal involvement.[4]

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