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Azathioprine-induced acute generalized exanthematous pustulosis in a woman with autoimmune hepatitis

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Consent for publication: the patient gave consent for their photographs and medical information to be published with the understanding that this information may be publicly available.

Availability of data and materials: data supporting the findings of this study are available from the corresponding author upon reasonable request.

Abstract

Acute generalized exanthematous pustulosis (AGEP) is a severe cutaneous drug reaction characterized by sterile pustules on erythematous skin. Azathioprine (AZA)-induced AGEP is rare, with few cases documented. We report a 50-year-old female with autoimmune hepatitis who developed a widespread pustular rash five days following the beginning of AZA therapy. Histopathology confirmed subcorneal pustules accompanied by eosinophilic infiltrates, indicative of AGEP. The discontinuation of AZA and systemic corticosteroids resulted in swift remission. This instance highlights the significance of prompt identification and discontinuation of medication to prevent adverse consequences.

Introduction

Acute generalized exanthematous pustulosis (AGEP) is a rare, severe, acute cutaneous adverse reaction defined by the emergence of many non-follicular, sterile pustules on a background of edematous erythema. Antibiotics, antifungals, the calcium channel blocker diltiazem, and antimalarials are the most common medications that cause AGEP.[1] Azathioprine (AZA), an immunosuppressant frequently employed in autoimmune disorders, is an infrequent initiator. Timely recognition and cessation of the causative medication are crucial for effective therapy. This example illustrates an AZA-induced AGEP manifestation, enriching the current literature.

Case Report

A 50-year-old female presented to the dermatology outpatient clinic with a non-pruritic pustular rash on erythematous skin affecting the trunk and limbs (Figure 1). The eruption initially manifested on the abdomen seven days earlier and was accompanied by fever. The patient had a recent history of autoimmune hepatitis treated with prednisone (0.7 mg/kg/day). In recent weeks, she had been gradually reducing the prednisone dosage. AZA 50 mg/day was initiated as an adjunct therapy twelve days before the onset of the rash. No personal or familial history of psoriasis was reported, and there were no recent changes in over-the-counter drugs.

A physical examination revealed numerous tiny, non-follicular, superficial pustules on erythematous and edematous plaques on her trunk and limbs. Palms of the hands, soles of the feet, and mucous membranes were spared. Blood tests indicated increased levels of C-reactive protein (CRP: 9.37 mg/dL) and erythrocyte sedimentation rate (ESR: 87 mm/h). The bacterial culture obtained from the pustular swab gave negative results. A skin biopsy from the abdomen region was obtained for histological examination (Figure 2).

Histopathological examination showed a large subcorneal pustule filled with neutrophils, foci of neutrophilic spongiosis in the adjacent epidermis, and prominent subepidermal edema (Figure 2). An intense perivascular and interstitial mixed inflammatory infiltrate, with lympho-histiocytes, neutrophils and eosinophils was observed in the superficial and mid dermis, confirming AGEP. Eosinophilic infiltrates further supported a drug-induced reaction.

AZA was discontinued at the time of the first dermatologic evaluation due to clinical suspicion of AGEP, and the prednisone dose was subsequently increased to 1 mg/kg/day. The pustular eruption began to regress within a few days and completely resolved within two weeks, leaving behind post-inflammatory erythematous macules. The resolution was accompanied by the typical desquamation phase, as expected in AGEP (Figure 3).[2] No recurrence of the lesions was observed.

Discussion and Conclusions

AGEP is rare, with an estimated incidence of 1 to 5 occurrences per million annually.[3] It predominantly affects females, with an average onset age of 57.8 years. Fever is a prevalent concomitant symptom and can assist in distinguishing AGEP from other pustular disorders.[1]

The eruption usually manifests within hours or days after drug exposure and disappears spontaneously within one to two weeks following drug cessation.

Three prior examples of AZA-induced AGEP have been documented in the literature: one involving a patient with pemphigus foliaceus (20 days until onset),[4] another with ulcerative colitis (4 days),[5] and a third with granulomatosis with polyangiitis (8 days).[6] Our case manifested within five days following the introduction of AZA.

The differential diagnoses for AGEP include generalized pustular psoriasis (GPP), bacterial folliculitis, and miliaria pustulosa. GPP frequently resembles AGEP but usually manifests in individuals with a history of psoriasis or psoriatic arthritis. Histologically, GPP lacks the eosinophilic infiltrates characteristic of AGEP. Bacterial folliculitis can be ruled out through negative cultures, while miliaria pustulosa, resulting from sweat duct obstruction, is limited to intertriginous regions and does not exhibit systemic involvement.

Treatment of AGEP is predominantly supportive, with medium-potency corticosteroids or systemic corticosteroids administered for moderate-severe cases.[7] Complications, including hemodynamic instability, are infrequent.

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Figure 1. Multiple small, superficial, non-follicular pustules on an erythematous and edematous base are distributed over the anterior trunk (**A**), back (**B**), and upper limbs. The close-up view (**C**) shows clusters of pinpoint pustules on inflamed skin.

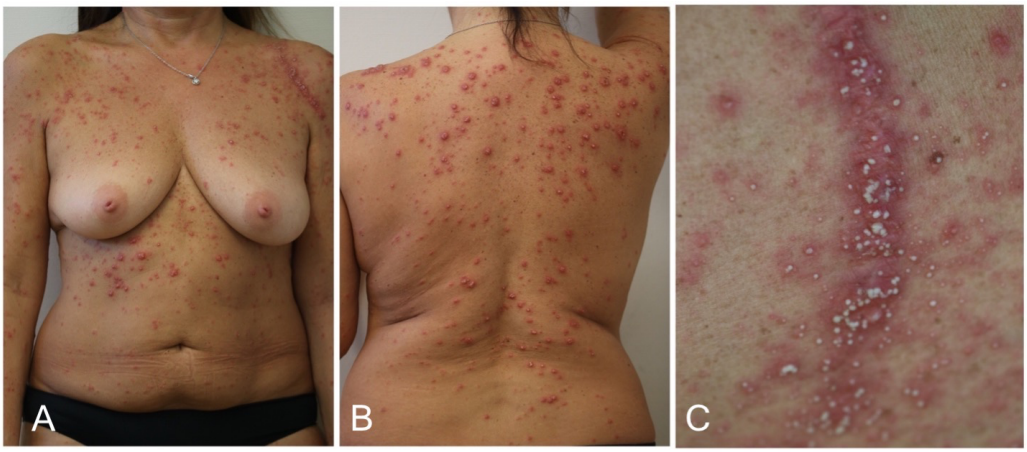

Figure 2. Large subcorneal pustule filled with predominantly neutrophils associated with prominent subepidermal edema. An intense dermal perivascular and interstitial mixed inflammatory infiltrate, with lympho-histiocytes, neutrophils, and eosinophils, is observed (inset). Hematoxylin and eosin stain, original magnification 4x, scale bar 150µ; inset: original magnification 40x, scale bar 25 µm.

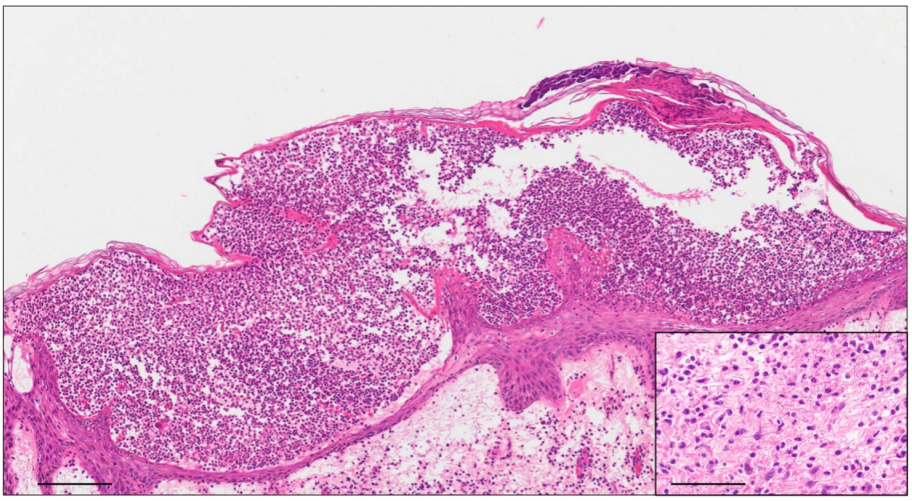

Figure 3. Resolution phase of the eruption. Scattered post-inflammatory erythematous macules are visible on the upper back, corresponding to previously involved areas.