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Marginal corneal infiltrates as an ocular manifestation of acute generalized exanthematous pustulosis

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ABSTRACT

Purpose: To report a case of keratoconjunctivitis with marginal corneal infiltrates in a patient with acute generalized exanthematous pustulosis (AGEP) secondary to trimethoprim-sulfamethoxazole.
Observations: A 63-year-old female presented with a diffuse pustular skin rash and bilateral keratoconjunctivitis with marginal corneal infiltrates. Skin biopsy led to the diagnosis of AGEP secondary to trimethoprim-sulfamethoxazole use. Treatment of the ocular findings with topical corticosteroids and lubrication led to near-full resolution after two weeks.
Conclusions and Importance: To the best of our knowledge, this is the first reported association between AGEP and keratoconjunctivitis with marginal corneal infiltrates. A hypersensitivity reaction to a foreign antigen is implicated in the pathogenesis of both AGEP and sterile marginal infiltrates, and we suggest that the patient's underlying hypersensitivity process associated with AGEP accounted for the ocular findings.

1. Introduction

Acute generalized exanthematous pustulosis (AGEP) is a rare skin reaction characterized by the acute onset of fever and a sterile, pustular rash that affects the limbs, trunk, face, and—less frequently—mucosal membranes.[1] It occurs as a result of medication in approximately 90 % of cases and may also follow viral infection, venom exposure, or mercury exposure. The most frequently associated medications are beta-lactam antibiotics, although other reported drug causes include sulfonamides, tetracyclines, antifungals, anticonvulsants, calcium channel blockers, and hydroxychloroquine. It is thought to be mediated by T cell-mediated keratinocyte apoptosis and subsequent recruitment of neutrophils, and histopathologic findings consistent with this underlying pathophysiology are helpful to confirm the diagnosis.[2–4]

Characteristically, AGEP develops within 24–48 hours of drug exposure with pinhead-sized pustules superimposed on edematous erythematous plaques. It initially affects the face or flexural regions before spreading to involve the trunk and limbs within a matter of hours. Fever and pruritus are frequent features; uncommonly, it will present with purpura, blisters or target-like lesions. AGEP reportedly involves mucosal membranes in about 20 % of cases. When it does involve mucosal membranes, it is typically mild and confined to the lips or buccal mucosa. Rarely, systemic involvement occurs with liver, kidney, and/or lung involvement.[2,3,5]

AGEP is not known to significantly affect the eye. In our review of the literature, we found that prior reports of AGEP include descriptions of periocular skin involvement and mild conjunctival irritation and/or injection; however, it has not been reported to involve the cornea.[3,5,6] We describe a patient with acute generalized exanthematous pustulosis who presented with bilateral keratoconjunctivitis with marginal corneal infiltrates that responded well to treatment with topical corticosteroids.

2. Case report

A 63-year-old African-American female with a past medical history of hypertension, obesity, and pre-diabetes presented to the emergency department with nine days of a pustular skin rash and three days of bilateral eye pain and redness. She reported a history of occasional eye redness and irritation, otherwise she has no past ocular history including surgery, contact lens use, or atopy. A few hours prior to the onset of her skin rash, she was given trimethoprim-sulfamethoxazole for a urinary tract infection. Review of systems was positive for subjective fever, headache, cough, and dry mouth. In the emergency department, she was afebrile with an unremarkable complete blood count and

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comprehensive metabolic panel. On exam, she had multiple small erythematous pustules on her extremities and trunk, sparing the face, palms, and soles (Fig. 1A). On ophthalmologic exam, visual acuity was 20/20 in both eyes, pupils were normal, and intraocular pressure (IOP) was 14 in the right eye and 12 in the left eye. Slit-lamp exam revealed bilateral sectoral conjunctival injection (2A), inferior gelatinous white limbal corneal infiltrates without overlying epithelial defect, and diffuse punctate epithelial erosions and tear film irregularities in both eyes, more severe in the right eye (Fig. 2B/D) than the left (Fig. 2C/E). There was no significant papillary or follicular conjunctival reaction. Anterior chamber was without cell or flare. The remainder of her ocular exam, including a dilated fundus exam, was normal. The corneal infiltrates were assumed to be sterile due to the bilateral nature and intact epithelium, and she was started on prednisolone acetate QID as well as lubrication with erythromycin ointment TID in both eyes. For her skin rash, she was started on triamcinolone 0.1 % ointment BID.

A skin punch biopsy of her left thigh demonstrated acanthosis, mild spongiosis, and subcorneal and intraepidermal vesicles with neutrophils, as well as a dermal superficial perivascular lymphohistiocytic infiltrate with rare eosinophils (Fig. 1B). In conjunction with her clinical history, the dermatology service felt the findings were most compatible with acute generalized exanthematous pustulosis. Further laboratory workup, including assays for COVID-19, monkey pox, tuberculosis, syphilis, and HIV, were normal.

Over the next two days, her eye pain resolved and her exam demonstrated a decrease in injection and both size and number of the limbal infiltrates. On her follow-up exam two weeks later, her visual acuity remained stable at 20/25 in both eyes, and exam demonstrated further improvement, with near-resolution of surface irregularity and only few limbal opacities remaining. She achieved similar remission of her dermatologic findings. Unfortunately, the patient has since been lost to follow-up.

3. Discussion

AGEP is a rare dermatologic diagnosis, with a reported incidence of one to five cases per million per year. Our review of the literature revealed three prior reports of AGEP with documented ocular findings: one report with periorbital erythema and desquamation, and two reports with conjunctival injection.[4–6] Our patient with trimethoprim-sulfamethoxazole-induced AGEP exhibited a keratoconjunctivitis with marginal corneal infiltrates and severe surface irregularity that responded well to topical corticosteroids and lubrication.

Given our patient's bilateral and symmetric findings, we felt this was more likely an inflammatory rather than infectious process. The differential diagnosis for noninfectious marginal keratitis in the absence of any mechanical or toxic stimuli includes Staphylococcal marginal keratitis, vernal keratoconjunctivitis (VKC), atopic keratoconjunctivitis (AKC), and peripheral ulcerative keratitis (PUK). Our patient presented with limbal gelatinous infiltrates classically seen in VKC or AKC; however, she lacked the intense itching frequently seen in these conditions and denied any history of atopic conditions. The infiltrates seen in our patient were located at the limbus, without the characteristic clear zone of cornea between the limbus and infiltrate seen in Staphylococcus marginal keratitis. Furthermore, the major risk factor for Staphylococcus marginal keratitis is the presence of longstanding blepharitis, conjunctivitis, or meibomitis, and our patient denied any history of persistent dry eye, crusting, or irritation. Our patient did have significant scleral injection concerning for scleritis, which would increase suspicion for PUK associated with autoimmune diseases. However, the injected vessels were located superficially when moved with a cotton swab, lacked a blueish hue, and the patient did not complain of severe pain or significant tenderness on palpation as is usually seen in scleritis. Although she denied any known autoimmune history or significant review of systems, outpatient labs were ordered for ANA, ACE, lysozyme, RF, and CCP; however, the patient was lost to follow-up prior to obtaining these labs.

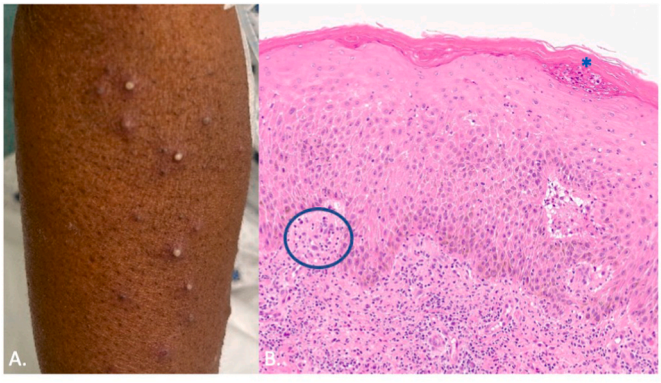

Fig. 1. External photographs of right forearm (A) and histopathologic findings of the left thigh using H&E staining at 10x demonstrating subcorneal pustule with neutrophils (*) in the epidermis and an infiltrate of lymphocytes, histiocytes, and eosinophils in the dermis (circle) (B).

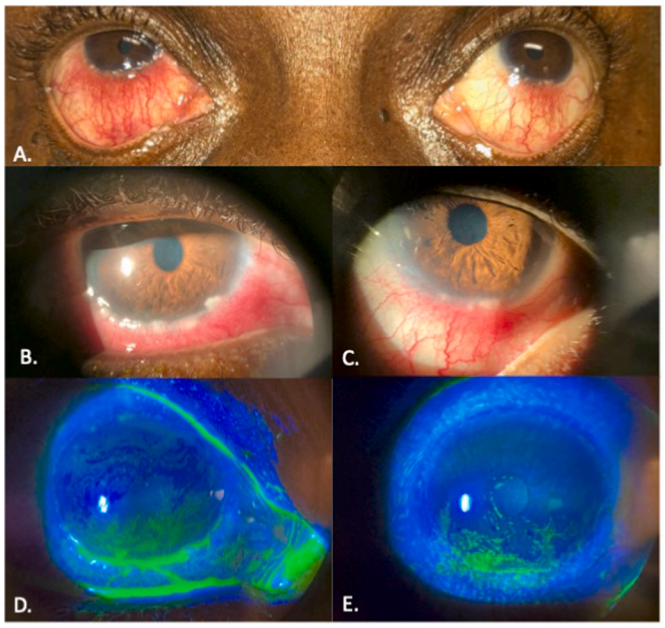

Fig. 2. External photograph demonstrating bilateral conjunctival injection (A) and slit-lamp photos and fluorescein staining of the right (B/D) and left (C/E) eyes, demonstrating conjunctival injection, white limbal corneal infiltrates, punctate epithelial erosions, and tear film irregularities without overlying epithelial defect.

We suspect that our patient's ocular findings are directly associated with her diagnosis of AGEP and represent an allergic response to trimethoprim-sulfamethoxazole. The inflammatory marginal infiltrates and tear-film abnormalities seen on her initial exam appear remarkably similar to those found in severe atopic keratoconjunctivitis (AKC), an allergic condition seen in patients with atopic dermatitis. AKC is a complex inflammatory disease thought to arise from both a type I (IgE-dependent) and type IV (T cell-mediated) hypersensitivity reaction leading to the infiltration of inflammatory cells into the conjunctival tissue.[7] The physiopathology of AGEP is thought to also be a type IV hypersensitivity reaction in which T cells proliferate in the dermis and epidermis, releasing cytokines that lead to the chemotaxis of neutrophils and the subsequent formation of sterile pustules.[1–3] We suggest that the same inflammatory response caused by our patient's AGEP was also the underlying cause of her ocular findings.

The histopathologic similarities between AKC and AGEP further

support our hypothesis that our patient's ocular findings are related to AGEP. The limbal infiltrates seen in AKC, known as Horner-Trantas dots, are composed of eosinophils, epithelial cells, and neutrophils.[8,7] Similarly, the histopathology of AGEP demonstrates intraepidermal neutrophilic pustules with dermal infiltrates of lymphocytes. Analyses of tears in patients with AKC have shown significantly increased eosinophils and neutrophil activity compared to controls, and we hypothesize that the accumulation of these inflammatory mediators in the tear film of our patients contributed to the inferior predilection of her ocular findings.[9,10]

AGEP has a mostly benign and self-limiting course, and treatment is based on the discontinuation of the causative agent, supportive care, and topical or systemic corticosteroids.[3] Our patient was treated with topical triamcinolone for her skin findings, and her ocular disease was managed with topical corticosteroids to both treat the sterile infiltrates and provide symptomatic relief, as well as aggressive lubrication for the ocular surface and tear-film irregularities. Both skin and eye findings significantly improved with this therapy.

In conclusion, this is a previously unreported ocular presentation of a rare dermatologic disease. A hypersensitivity reaction to a foreign antigen is implicated in the pathogenesis of both AGEP and sterile marginal infiltrates, and we hypothesize that an allergic inflammatory reaction associated with AGEP secondary to trimethoprim-sulfamethoxazole was the cause of our patient's ocular findings, which responded well to treatment with topical corticosteroids and lubrication.

Patient consent

Informed consent to publish the case report was obtained from the patient in a signed documented uploaded onto the Cleveland Clinic electronic medical record system.

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Authorship

All authors attest that they meet the current ICMJE criteria for Authorship.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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