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Generalized pustular figurate erythema: A newly delineated severe cutaneous drug reaction linked with hydroxychloroquine

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Abstract

A severe cutaneous drug reaction resembling acute generalized exanthematous pustulosis resulting from ingestion of hydroxychloroquine has been documented. It is distinguishable by its longer incubation period, more varied morphology with initially urticarial and later targetoid and arcuate plaques, recalcitrance to therapy and longer duration. Given the anticipated surge in the use of hydroxychloroquine due to its reported benefits in those with coronavirus disease 2019, specific recognition of this entity is pivotal. We delineate it as generalized pustular figurate erythema.

KEYWORDS

acute generalized exanthematous pustulosis, coronavirus, COVID-19, DRESS syndrome, drug rash, erythema multiforme, figurate erythema, hydroxychloroquine, SARS-2, SARS-CoV-2, Stevens-Johnson syndrome, Sweet syndrome, toxic epidermal necrolysis, urticaria

Severe potentially life-threatening cutaneous drug reactions are a huge concern, most specifically acute generalized exanthematous pustulosis (AGEP), Stevens-Johnson syndrome (SJS), toxic epidermal necrolysis (TEN), generalized bullous fixed drug eruption, and drug reaction with eosinophilia and systemic symptoms (DRESS) syndrome.[1-8] AGEP was originally misclassified as a form of pustular psoriasis; however, it is not associated with psoriasis.[9] AGEP is a severe cutaneous adverse reaction characterized by the rapid development of sterile nonfollicular pustules on an erythematous base.[2,3] It is usually attributed to drugs, antibiotics being the most common, with an onset typically within 48 hours of ingestion, often with an acute onset of fever and leukocytosis.

There is another rare acute severe generalized disorder, one usually characterized as AGEP, but with an onset of 2 to 3 weeks (range 4-27 days) rather 1 day after initial drug exposure, typically due to hydroxychloroquine, more severe, more difficult to treat, with a longer duration, and recognized as likely having a different pathogenic mechanism from the usual type of AGEP.[10] This perplexing disorder has been described as atypical AGEP,[11,12] recalcitrant AGEP,[13,14] pustular DRESS syndrome,[15] AGEP/SJS overlap,[16] AGEP/TEN overlap,[17,18] and Sweet's syndrome following hydroxychloroquine.[19-21] We delineate and highlight it as generalized pustular figurate erythema (GPFE). It can be due to a number of medications, but we now emphasize its association with hydroxychloroquine. This antimalarial drug commonly employed for a variety of rheumatic and dermatological disorders is now under evaluation as an antiviral agent against coronavirus disease 2019 (COVID-19).[22,23] More than 20 cases of GPFE from hydroxychloroquine have been described in the medical literature.

Clinical examination reveals an abrupt onset of a pruritic eruption representing a severe cutaneous drug reaction with fever and neutrophilic leukocytosis.[11-21] GPFE may be first evident as erythematous papules and plaques on the face with facial edema and widespread urticarial or edematous plaques scattered over the entire body, with development of nonfollicular pustules atop what evolve into erythematous and sometimes atypical targetoid erythema multiforme-like plaques converging into annular and arcuate patterns prominent on the trunk and extremities (Figure 1). Pustular erythema may develop irregularly along active borders. Erythema may fade with scaling, including on the palms and soles. Some cutaneous sloughing and excoriations may also be observed with blisters or erosions occasionally noted. There may be little or no mucosal involvement. Skin biopsy specimens may initially show mainly the changes of urticaria, but evolve into subcorneal and/or intraepidermal neutrophilic pustules sometimes with mild focal

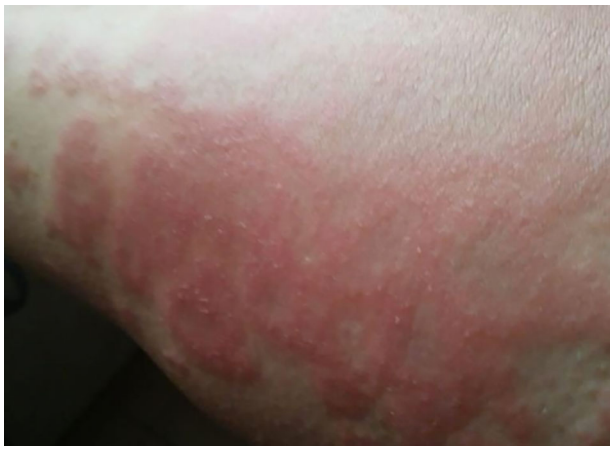

FIGURE 1 Hydroxychloroquine-induced GPFE with numerous nonfollicular pustules atop atypical targetoid plaques. GPFE, generalized pustular figurate erythema

acantholysis, exocytosis, spongiosis, and an edematous papillary dermis with a perivascular lymphocytic infiltrate with occasional neutrophils, eosinophils, and mast cells progressing into a dermal neutrophilic infiltrate. No vasculitis is anticipated.

Treatments have been varied.[11-21,24-26] The first line therapy is topical and systemic steroids, which may be followed by cyclosporine if GPFE is not responsive.[13,14,21] Other options include potent topical steroids with oral dapsone or etretinate.[25] Additional experience with GPFE and its treatment can be anticipated to surge as hydroxychloroquine becomes widely utilized in the COVID-19 pandemic.

CONFLICT OF INTEREST

The authors declare no potential conflict of interest.

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