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CASE REPORT

Hydroxychloroquine-Induced Erythema Multiforme in a Pregnant Female

Muhammad Imran, M.D.[1], Joseph Blackmon, M.D.[2], Julian Magadan III, M.D.[1], Garth Fraga, M.D.[3], Deede Liu, M.D.[2], Mehrdad Maz, M.D.[1]
University of Kansas Medical Center, Kansas City, KS
Department of Internal Medicine
[1]Division of Allergy, Clinical Immunology, and Rheumatology
[2]Division of Dermatology
[3]Department of Pathology and Laboratory Medicine

INTRODUCTION

Hydroxychloroquine (HCQ) is a disease-modifying antirheumatic drug that is used commonly as an immunomodulatory agent in the treatment of rheumatic diseases. It is considered a relatively safe drug. It is a pregnancy class C drug; however, years of retrospective and prospective clinical experience has shown that its administration does not lead to fetal teratogenicity.[1-5] Rarely, it can lead to retinal toxicity that can be prevented and detected by periodic ophthalmologic examinations.[3] The most common cutaneous adverse reaction of HCQ is skin hyperpigmentation or a typical cutaneous drug eruption. However, it also can cause rare and more significant dermatoses, such as erythema multiforme (EM) or erythema annulare centrifugum.[4] Erythema multiforme is an acute, self-limiting mucocutaneous hypersensitivity syndrome. Approximately 66% of patients who develop EM possess the HLA-DQB1*0301 26 allele, which is present in only 31% of healthy subjects.[6] We present a severe case of EM induced by HCQ in a pregnant patient.

CASE REPORT

A 20-year-old pregnant African-American female presented to the rheumatology clinic at 16 weeks of gestation for the evaluation of an elevated antinuclear antibody level, a malar rash, and concern for undiagnosed systemic lupus erythematosus (SLE). The patient met the American College of Rheumatology (ACR) classification criteria for SLE based on malar rash, painless oral ulcers, alopecia, strongly positive ANA of titer > 1280 speckled pattern, photosensitivity and arthritis which confirmed the diagnosis of SLE.[7] The patient also had positive SSA and SSB (anti-Ro and anti-La) antibodies. Hence, HCQ therapy was initiated as an immunomodulatory agent to manage the SLE and prevent its potential complications for the patient and the fetus.

A few days later, the patient presented to the emergency department with a painful, erythematous macular exanthem predominantly over the anterior and posterior aspects of her torso and upper extremities. Additionally, she had tense and flaccid bullae bilaterally on her breasts and chest. The patient had no evidence of mucosal involvement, although she developed vesicles on her cutaneous lips, forehead, and cheeks. Subsequently, she was admitted for further evaluation and pain management, with rheumatology and dermatology inpatient consultations.

During her hospitalization, the patient developed target lesions on her palms and upper extremities consistent with EM (Figures 1 and 2). The patient underwent a skin biopsy that confirmed the diagnosis (Figure 3). Infectious serologies and cultures, including those for herpes simplex virus (HSV) and *Mycoplasma pneumoniae*, were negative. She was not on any other medicine except HCQ. Due to the concern for potential toxic epidermal necrolysis in bullous lesions, the patient initially was started on intravenous immunoglobulin for four days. She was transitioned to oral prednisone, 40 mg daily, with a slow taper after skin biopsy confirmed diagnosis of EM. After initiation of prednisone therapy, her skin lesions improved with resolution of erythema and pain. She was discharged in stable condition on a steroid taper with resolving skin lesions.

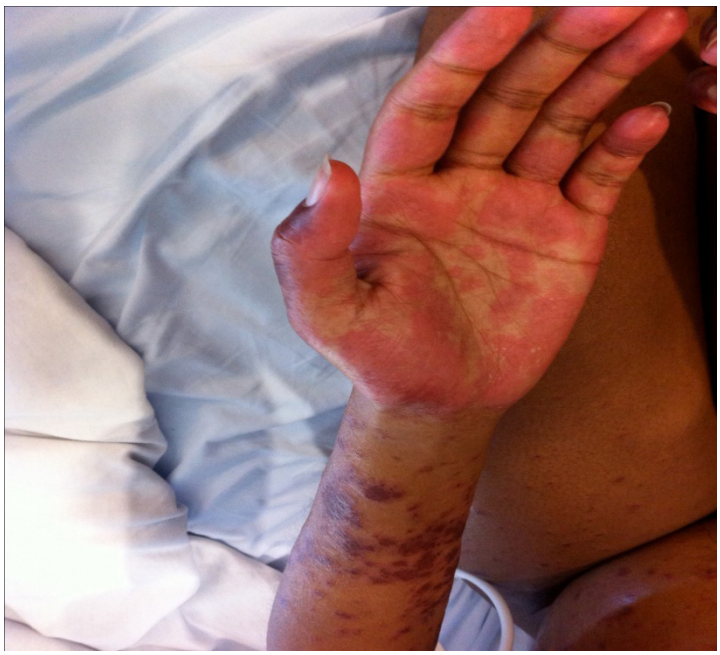

Figure 1. Diffuse, scattered erythematous macules coalesced into patches with islands of sparing on acral surface of left palm.

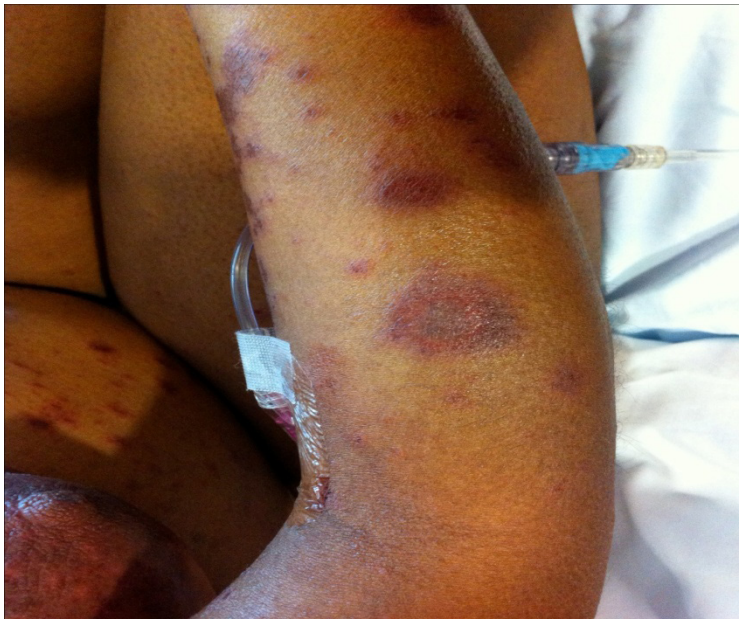

Figure 2. On day two, lesions began to form characteristic "typical" targetoid lesions including two concentric rings surrounding a central area of bullae and/or necrosis.

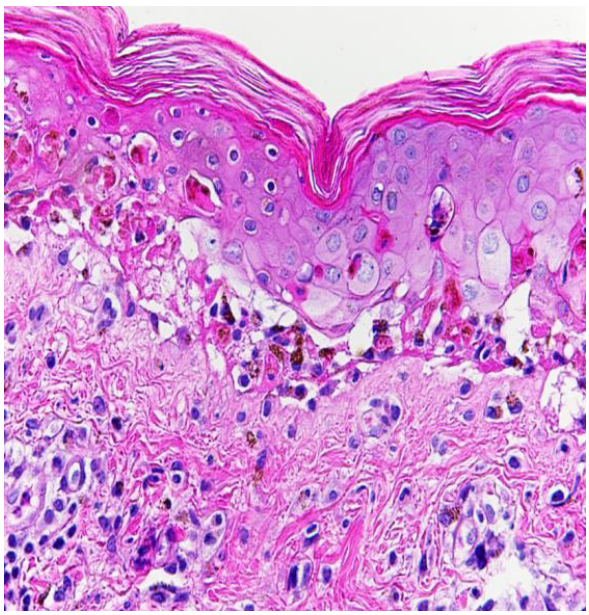

Figure 3. Skin biopsy demonstrated vacuolar interface lymphocytic dermatitis with ballooned and apoptic keratinocytes in the spinous layer, melanoderma and a normal corneum. Viral inclusions, deep dermatitis, eosinophils, and neutrophils were absent. Direct immunofluorescence was non-reactive for IgG, IgA, IgM, and C3.

DISCUSSION

Erythema multiforme, in its purest form, is an acute, self-limited but potentially recurrent skin disorder.[8] It is observed predominantly in young adults, rarely in childhood, and has a slight male preponderance but no racial bias. Austrian dermatologist Ferdinand von Hebra first described this condition in 1860.[9] The clinical hallmark of EM is the abrupt onset of typical target lesions forming within the first 24 hours. There may or may not be mucosal involvement. Clinically, the typical targets exhibit three distinct circles or "zones." The innermost circle often initially is dusky and followed centripetally by two other concentric rings. The central circle subsequently may develop into a bulla and/or crust later in the course of the disease. Additionally, atypical targets may be predominant, especially early in the course of the disease. Usually, there are only two different zones and there is generally a poorly defined border (< 3 cm in diameter).

Development of EM has been associated with herpes simplex virus (HSV) or *Mycoplasma pneumoniae* infections.[10] Rarely (<10% of cases), it is caused by drugs such as NSAIDS, sulfonamides, penicillin, antiepileptics, and antibiotics. According to the Medicines Control Agency, there have been four reports of EM since 1964 related to hydroxychloroquine use.[11] There is a single case report in the literature describing a case of erythema annulare centrifugum related to the use of hydroxychloroquine.[12] In addition, there is a report of acute generalized exanthematous pustulosis.[13] Furthermore, it is recognized that hydroxychloroquine can exacerbate psoriatic skin lesions,[14] an effect thought to be related to inhibition of epidermal transglutaminase activity.[15]

Most importantly, EM is to be differentiated from acute disseminated epidermal necrolysis, which includes Stevens–Johnson syndrome (SJS), toxic epidermal necrosis (TEN) and the SJS/TEN overlap.[16] In our case, there was a definite predilection for atypical targets upon the patient's presentation to the emergency room. The differential diagnosis was EM, SJS, and TEN. Our patient had no mucosal involvement, a variable that essentially is mandatory when diagnosing a patient with SJS or TEN. Also, the skin biopsy was consistent with EM, which ruled out the possibility of SJS, TEN, or bullous SLE. To the best of our knowledge, this is the first case of erythema multiforme due to hydroxychloroquine in a pregnant patient.

For clinicians, it can be a daunting task to make a clear and concise diagnosis when a patient presents with an abrupt onset of painful, blistering, and/or exfoliative skin lesions. First and foremost, a thorough history must be obtained. Medications and the duration or timing of exposure to medications are important when gathering the patient's history. One also must conduct a comprehensive review of systems and tests to rule out potential infectious etiologies that could cause an EM eruption, including but not limited to HSV or *mycoplasma pneumoniae*. Next, obtain a thorough physical examination of the patient's skin, including the mucosal surfaces of the ocular, oropharyngeal and genital surfaces. Skin biopsy for both permanent and frozen sections may differentiate between SJS/TEN, EM, bullous LE, or a bullous drug eruption. Even then, the diagnosis often cannot be made on pathology alone, hence the importance of the role a detailed history and physical examination play in securing an accurate diagnosis.

CONCLUSIONS

Overall, hydroxychloroquine has a minimal and acceptable side effect profile. It can be used in pregnancy, but its potential serious cutaneous side effects including SJS, TEN and EM should be considered prior to initiation. This extraordinary case highlights promising new medical management of medication-induced erythema multiforme with intravenous immunoglobulin and underscores the value of prompt diagnosis and supportive care. Prognosis reportedly is better for patients transferred promptly to a burn unit or intensive care unit.[17] For unknown reasons, our patient was treated in the general medicine unit. In an age of increasing patient poly-pharmacy, it is of paramount importance to consider all medication-induced side effects, both common and severe.

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