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Hydroxychloroquine-induced erythema multiforme

Nour Abou Assalie, MD¹, Robert Durcan, MB.BCh.BAO.LRCSI², Laura Durcan, MD³, and Michelle A. Petri, MD, MPH³

¹Department of Medicine, Saint Agnes Hospital, Baltimore, MD, USA. ²Beaumont Hospital, Dublin, Ireland. ³Hopkins Lupus Center, Department of Medicine, Johns Hopkins University, Baltimore, MD, USA.

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To the Editor

Hydroxychloroquine is the cornerstone of medical therapy in systemic lupus erythematosus. It has been shown to reduce lupus flares¹, delay the onset of lupus², and to increase survival in lupus patients³. Hydroxychloroquine also has a favorable effect on hyperlipidemia⁴, reduces the risk of thrombosis⁵, improves the outcome of lupus nephritis⁶, may delay renal damage⁷, reduces the risk of developing neuropsychiatric lupus⁸, and reduces the risk of developing coronary artery calcifications⁹. The main complication of hydroxychloroquine use is retinopathy with a risk of 1/5000 after the first 5 years¹⁰. Cutaneous adverse reactions to hydroxychloroquine have been described, including: acute generalized exanthematous pustulosis^{11, 12}, Stevens-Johnson syndrome¹³, and toxic epidermal necrolysis^{14–16}. Here we report a case of hydroxychloroquine-induced erythema multiforme (after 12 days of exposure) in a 25 year old woman with lupus.

Case Presentation

A 25 year old Caucasian woman with a past medical history of Hashimoto thyroiditis and autoimmune hemolytic anemia presented with two-day history of pruritic, erythematous rash. The lesions first appeared on her back and trunk but rapidly spread to her extremities and face. She also complained of fatigue, anorexia and chills. She had been started on hydroxychloroquine 200 mg twice daily 12 days prior to presentation for her diagnosis of lupus erythematosus. She had met four criteria of the SLICC classification criteria for SLE diagnosis¹⁷ which were: Coombs-positive hemolytic anemia, positive ANA, low complement, and positive anti-dsDNA.

Corresponding author: Nour Abou Assalie, MD, 900 S. Caton Avenue. PO Box: 198, Baltimore, MD 21229, Tel: 410-368-8858, Fax: 410-368-3525, nourabouassalie@gmail.com.

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On admission, she was noted to have a temperature of 104 degrees with otherwise normal vital signs. Her skin examination showed flat, erythematous, morbilliform lesions on the chest, abdomen, back, face involving the nasal folds, arms and legs. Small ulcers were found on her hard palate. Confluent superficial ulcers were also seen on her labia major. Her laboratory work-up including white blood cell count, eosinophil count, hemoglobin, renal function, urinalysis and complement level were all normal. By the next day, she had multiple new lesions with targetoid morphology suggestive of erythema multiforme (Figure 1).

Infectious work-up including blood and urine cultures was negative. Titers for other common etiologies for erythema multiforme including Herpes simplex virus and Mycoplasma Pneumonia were also negative. Skin biopsy showed interface dermatitis and eosinophil infiltrates. This latter finding suggested an allergic process such as a drug reaction.

Hydroxychloroquine was stopped from the day of admission. Methylprednisolone 1 gm IV daily was given for a three-day course. A gradual improvement of the exanthema was noted. However new target lesions developed as corticosteroids were tapered, prompting an increase in the dose of oral prednisone to 1 mg/kg daily for 3 days followed by a very slow taper. At the time of discharge, most of the lesions had developed superficial desquamation, and a complete resolution of the oral and vaginal ulcers was noted. After two weeks of corticosteroid taper, follow up at the clinic showed normal skin without any lesions.

Erythema multiforme is a reactive mucocutaneous disorder in a disease spectrum that includes erythema multiforme minor, erythema multiforme major, Stevens Johnson syndrome, and toxic epidermal necrolysis. In spite of the significant differences between these four entities, they all share the pathogenesis of cytotoxic immunologic process. Many factors have been described in the literature as precipitators of erythema multiforme. Among those factors, infectious agents and drugs are the most reported ones¹⁸. Rowell et al described an association between lupus erythematosus and erythema multiforme-like skin lesions in 1963¹⁹. This association was reported with the presence of certain immunological disturbances in an entity that was named as Rowell's syndrome. This association was reviewed by Shteyngarts et al in 1999²⁰ who showed that such entity was not reproducible.

Our patient had systemic lupus erythematosus, meeting four of the SLICC classification criteria¹⁷. She developed erythematous target lesions, the most dominant lesions of erythema multiforme, within two weeks of the initiation of hydroxychloroquine treatment. The lesions were typical targets with well-defined borders and three distinct zones consisting of two concentric rings around a central disk²¹. She met the criteria for the diagnosis of erythema multiforme major with mucous membranes involvement. Common infectious etiologies for erythema multiforme were excluded. Interface dermatitis found in the skin biopsy is a nonspecific inflammation at the dermis-epidermis junction that can be found in many connective tissue diseases, whereas eosinophil infiltrates suggested an allergic drug-induced exanthema. Hydroxychloroquine was the most likely culprit for her erythema multiforme.

This case was important because it demonstrated a rare cutaneous side effect of hydroxychloroquine. Perez-Ezquerria et al reported the first case of hydroxychloroquine-

induced erythema multiforme in 2006²². Other cutaneous adverse reactions of hydroxychloroquine have also been reported (Table-1)^{11–16, 22}. Two out of the seven reported cases of hydroxychloroquine induced cutaneous adverse reactions were fatal. In our case, the patient's skin lesions resolved with high dose and slow taper course of steroid treatment.

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Figure 1. shows the patient's exanthema on day two of admission. The typical targetoid lesions of erythema multiforme are well demonstrated.

Table 1

Reported cases of hydroxychloroquine-induced cutaneous adverse reactions

Reference	Hydroxychloroquine- induced adverse reaction	Underlying connective tissue disease	Treatment	Outcome
Cameron et al 2014	Eruptive toxic epidermal necrolysis	SLE	Intravenous immunoglobulin	Death
Park et al 2010	Acute generalized exanthematous pustulosis	Dermatomyositis and polyarthralgia	Intravenous corticosteroid followed by oral prednisone.	Resolution
Lateef et al 2009	Acute generalized exanthematous pustulosis which evolved to toxic epidermal necrolysis	SLE	Intravenous corticosteroid and intravenous immunoglobulin	Resolution
Callaly et al 2008	Toxic epidermal necrolysis	Sjogren's syndrome	Intravenous corticosteroid	Resolution
Perez-Ezquerro et al 2006	Erythema multiforme	Ankylosing spondylitis	Intravenous corticosteroid and antihistamines	Resolution
Leckie et al 2002	Stevens-Johnson syndrome	Rheumatoid arthritis	Intravenous and topical corticosteroid	Resolution
Murphy et al 2001	Toxic epidermal necrolysis	Rheumatoid arthritis	NR	Death

Table-1 summarizes the reported cases in the literature of hydroxychloroquine-induced cutaneous adverse reactions in chronological order. Treatment, outcome and the underlying connective tissue diseases associated with these cases are also listed.

NR not reported; SLE systemic lupus erythematosus.