A case series of hydroxychloroquine exacerbating the dermatomyositis rash

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Abstract

Hydroxychloroquine (HCQ) is an antimalarial agent that is commonly used in the management of rheumatic skin disease. Few reports exist documenting exacerbation of dermatomyositis (DM) related to HCQ. Herein, we describe three adult patients with worsening DM cutaneous disease after starting HCQ and resolution or improvement with cessation. The time to exacerbation ranged from two weeks to nine months after the initiation of HCQ 400mg/day. Two of the three patients had antibodies to transcription intermediary factor 1γ (TIF1γ) and the other had antibodies to anti-nuclear matrix protein 2 (NXP2). After discontinuation of HCQ, the time to improvement or resolution of cutaneous symptoms ranged from six weeks to six months. Hydroxychloroquine may be associated with worsening cutaneous features in DM. In patients who are not improving despite escalation of immunosuppressive medications, or are worsening, we recommend a trial of discontinuing HCQ.

Keywords: adverse effect, autoimmune, dermatomyositis, hydroxychloroquine, rheumatology

Introduction

Dermatomyositis (DM) is an uncommon autoimmune disease characterized by skin changes with or without proximal symmetric muscle weakness [1]. Classic cutaneous manifestations include confluent macular violaceous erythema (CMVE) and/or poikiloderma overlying the hands (Gottron sign), anterior chest (V-sign), upper back and shoulders (shawl sign), lateral thighs (holster sign), or periorbital area (heliotrope rash). Other characteristic findings include violaceous flat-topped papules overlying hand joints (Gottron papules) and ragged cuticles with or without overgrowth (Samitz sign). Patients with DM may have circulating autoantibodies with diagnostic and prognostic utility [2].

Hydroxychloroquine (HCQ) is an antimalarial medication that is commonly used for treatment of DM. However, adverse cutaneous reactions are not uncommon. Approximately 21 unique dermatologic reactions associated with HCQ are described; the most common are drug eruption (e.g., maculopapular, erythematous, urticarial) and cutaneous hyperpigmentation [3]. Wolstencroft et al. found that HCQ-associated skin eruption developed in 20.7% of patients with DM [4]. The authors noted that some patients experienced acute worsening of their DM-associated skin disease after HCQ. However, in many cases they were unable to clearly differentiate between a hypersensitivity drug reaction and acute worsening of DM [4]. Bloom and colleagues reported two cases of juvenile DM, in which HCQ seemed to exacerbate the DM rash [5]. Herein, we present three cases of adult DM whose cutaneous disease was exacerbated by HCQ and improved with discontinuation.

Case Synopsis

Case 1 is a 30-year-old woman seen in dermatology clinic for DM. The patient had calcinosis cutis, arthralgias, and serologies demonstrating a positive low-titer antinuclear antibody, β2 glycoprotein antibodies (131U/ml), and anti-nuclear matrix protein (NXP2) antibodies. Physical examination showed scattered, firm nodules and plaques over the extremities, lower abdomen, and buttocks. Cancer work-up was negative for underlying malignancy. She was started on HCQ 400mg/day and diltiazem 180mg/day for biopsy proven calcinosis cutis (**Figure 1**). Four months later, she presented with faint violaceous patches over the dorsal metacarpal phalangeal (MCP) and proximal interphalangeal (PIP) joints, poikilodermatous patches over the upper back, and patchy erythema over the bilateral malar cheeks involving the melolabial folds (**Figure 2**). Dilated loops were newly identified on nailfold capillaroscopy. No biopsy was performed during the dermatomyositis exacerbation. Her cutaneous symptoms progressed despite adding methotrexate 20mg/week and potent topical corticosteroids. Hydroxychloroquine was discontinued after 12 months due to suspicion this was contributing to her worsening cutaneous eruption. Two months after stopping HCQ the erythema overlying her MCPs and thefacial rash resolved.

Case two is a 59-year-old man with a history of DM with anti-transcription intermediary factor one

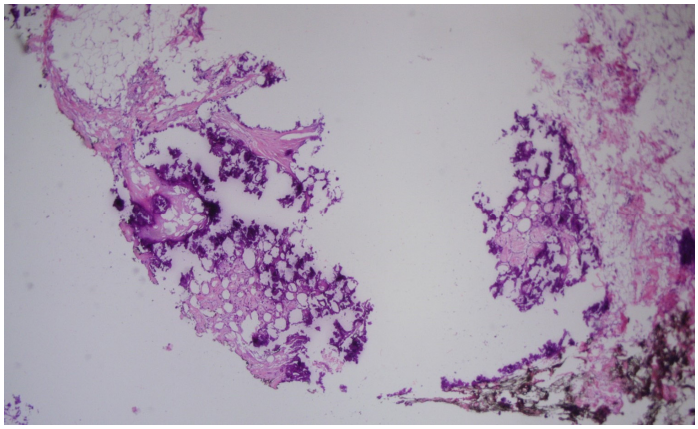

Figure 1. *Case 1 pathology. Biopsy taken from the left arm prior to dermatomyositis exacerbation demonstrating abundant calcium deposition, fat necrosis, and fibrosis within the subcutis. Increased mucin and pockets of lymphoplasmacytic inflammation also seen within subcutaneous fat lobules. H&E, 40×.*

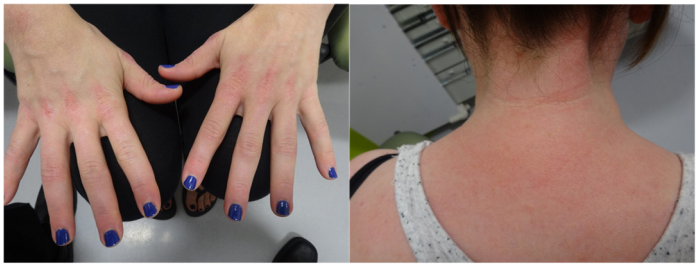

Figure 2. *Case 1 clinical presentation. Dermatomyositis exacerbation with bilateral malar rash, Gottron papules on hand, and poikilodermatous patches over the upper back.*

(TIF1γ) antibodies who presented to dermatology clinic for management of DM-related skin disease. His DM was diagnosed nine months prior and had been managed with high-dose prednisone and methotrexate 20mg/week. Cancer work-up at the time of diagnosis found no internal malignancy. His examination showed mild diffuse CMVE involving the malar cheeks, V-neck, and upper back as well as Gottron papules on the dorsal hands. He was started on HCQ 400mg/day. One month later, he was seen in follow up and reported discontinuing HCQ after two weeks due to significant spreading of rash. His examination demonstrated extension of shawl sign to the lower back with flagellate erythema and new onset holster sign (**Figure 3**). He also developed new Gottron sign and linear extensor erythema involving the dorsal hands. Histopathology demonstrated superficial perivascular infiltrate along with mild epidermal atrophy (**Figure 4**). Six weeks after discontinuing HCQ, his cutaneous symptoms were similar to his pre-HCQ exposure examination.

Case three is a 54-year-old female with a history of resected carcinoid tumor and Sjogren syndrome

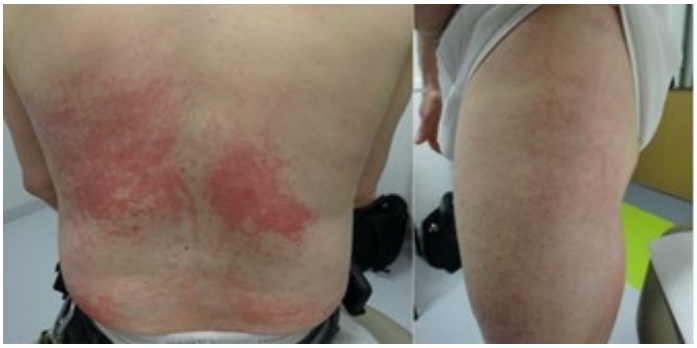

Figure 3. *Case 2 clinical presentation. Dermatomyositis exacerbation with new involvement of lower back with flagellate erythema, and new holster sign, four weeks after starting hydroxychloroquine.*

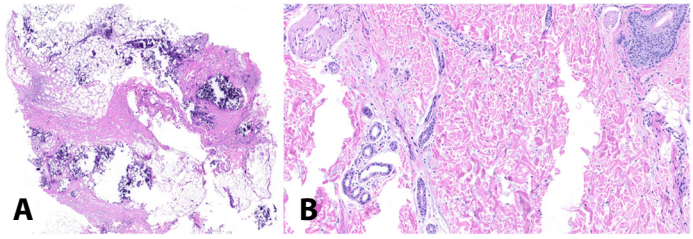

Figure 4. *Case 2 H&E histopathology.* ***A)*** *Biopsy from the right knee demonstrating sparse superficial perivascular mononuclear infiltrate with associated focal effacement of the rete pattern and mild epidermal atrophy, 40×.* ***B)*** *At medium power, an obvious but pauci-inflammatory vacuolar interface dermatitis is noted, with cytoid bodies and pigment incontinence present in the papillary dermis subjacent to the effaced and atrophic epidermis, 100×.*

who presented to dermatology clinic for ten months of persistent rash. She initiated HCQ 400mg/day approximately nine months prior to onset of rash. On examination, she had pink-violaceous thin edematous plaques in a scattered distribution over the buttocks (**Figure 5A**) and lateral thighs (**Figure 5B**). A skin biopsy showed superficial and deep perivascular lymphoplasmacytic inflammation with mucin and myositis-specific antibody panel was positive for anti-TIF1γ antibodies. The patient had recalcitrant skin disease and throughout her course was trialed on potent topical corticosteroids, methotrexate, azathioprine, mycophenolate mofetil, cyclosporine, and quinacrine. She had minimal improvement on these agents and developed adverse effects necessitating discontinuation. Her cutaneous symptoms progressed to involve the chest (**Figure 5C**) and dorsal arms (**Figure 5D**, **E**).

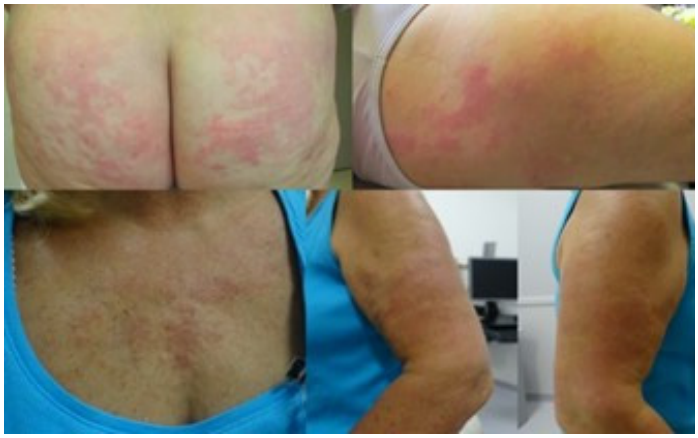

Figure 5. *Case 3 clinical presentation. Dermatomyositis exacerbation 1.5 years after initiation of hydroxychloroquine with violaceous thin edematous plaques over the buttocks, right thigh, chest, and arms.*

Cancer work-up revealed no underlying malignancy or recurrence of carcinoid. Upon histopathologic evaluation, basophilic calcific nodules were seen in the deep dermis and subcutis (**Figure 6**). Due to suspicion that HCQ may be contributing to her worsening skin disease, it was discontinued and her eruption resolved after six months.

Case Discussion

Hydroxychloroquine is often used as a first-line therapy for dermatomyositis. Although HCQ-induced drug eruption has been well documented in literature, few have described associated DM rash exacerbation/initiation with HCQ. Bloom et al. reported the first two cases of juvenile DM, in which HCQ seemed to exacerbate/initiate the DM rash [5]. One patient developed worsening of Gottron papules and a diffuse erythematous, scaly eruption over the thighs, pretibial skin, and posterior neck. The other experienced exacerbation of purple-red plaques on the face, neck, and arms and a new erythematous, pruritic rash in the axillae. Both patients saw improvement within days to weeks of discontinuing HCQ. More recently, a retrospective cohort of HCQ-associated skin eruptions identified five patients with a DM flare. However, authors declared it difficult to differentiate worsening DM from drug eruption [4].

Our cases are similar to those in the report by Bloom [5], in which patients presented with an exacerbation of characteristic lesions in DM including development and/or worsening of heliotrope rash, Gottron sign, Gottron papules, and/or nailfold capillary changes. The time to exacerbation ranged from two weeks to nine months after initiation of HCQ and time to improvement/resolution ranged from six weeks to six months after discontinuation of HCQ (**Table 1**).

It is difficult to establish if the adverse event described was solely due to HCQ as DM can have a waxing and waning course. According to WHO-UMC Causality Categories, the association is probable/likely given the reasonable time relationship of clinical symptoms to HCQ intake and improvement/resolution of symptoms after HCQ discontinuation [6].

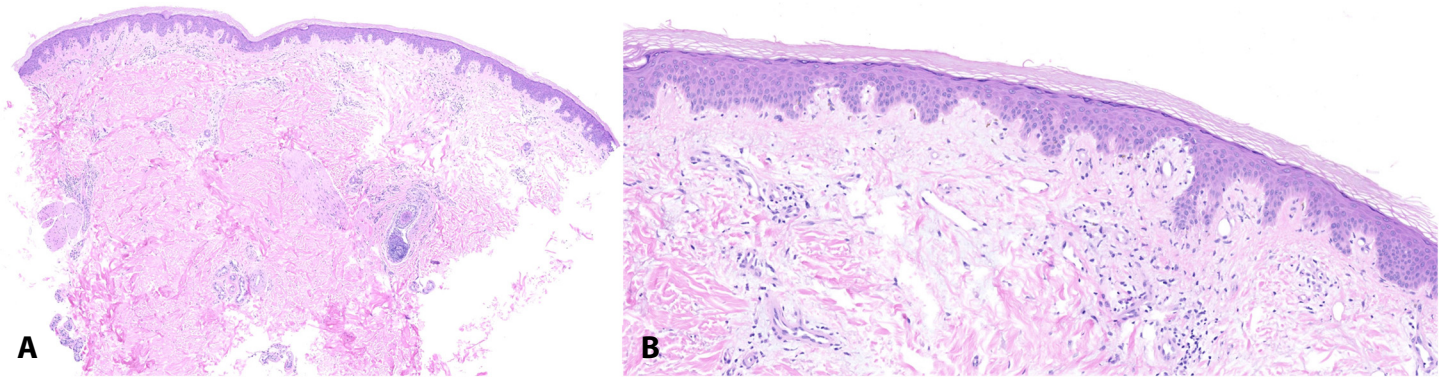

Figure 6. *Case 3 H&E histopathology.* ***A)*** *In the deep dermis and subcutis, numerous basophilic calcific nodules are seen, with focal associated fat necrosis and dystrophic calcification, 40×.* ***B)*** *On higher magnification, abundant interstitial mucin is seen in the dermis, 100×.*

Table 1. *Summary of dermatomyositis exacerbations.*

	Case 1	Case 2	Case 3
Age at presentation	30 years	59 years	54 years
Sex	Female	Male	Female
Medical History	DM with panniculitis and dystrophic calcinosis cutis	DM, type II diabetes mellitus, hypertension, hyperlipidemia	DM, resected carcinoid tumor, Sjogren Syndrome, seronegative RA, GERD
Medications at time of exacerbation	HCQ, diltiazem	HCQ, methotrexate, amlodipine, aspirin, atorvastatin, cetirizine, glipizide, prednisone, trimethorpim-sulfamethoxazole	HCQ, methotrexate
Myositis	Absent	Present	Absent
Myositis-specific antibodies	anti-NXP2	anti-TIF1γ	anti-TIF1γ
Time to DM exacerbation	4 months	2 weeks	9 months
Clinical features of exacerbation	New heliotrope sign, Gottron's sign involving MCP and PIP joints, poikilodermatous patches over upper back, facial erythema involving melolabial folds, dilated capillary loops on nailfold capillaroscopy	Extension of shawl sign throughout back with flagellate erythema and new holster sign	V-sign, shawl sign, faint Gottron's sign, holster sign
Time to improvement/ resolution after discontinuation of HCQ	2 months	6 weeks	6 months

anti-NXP-2, anti-nuclear matrix protein 2; anti-TIF1γ, anti-transcription intermediary factor 1γ; DM, dermatomyositis; GERD, gastroesophageal reflux disease; HCQ, hydroxychloroquine; MCP, metacarpophalangeal; PIP, proximal interphalangeal; RA, rheumatoid arthritis.

Conclusion

Herein, we describe three adult patients with exacerbation/initiation of the DM rash following HCQ therapy and resolution or improvement with cessation of their medication. We believe this phenomenon may be more common than reported in the current literature. In patients who are not improving despite escalation of immunosuppressive medications, or are developing worsening skin lesions, we recommend a trial of discontinuing HCQ prior to further escalation of immunosuppressive medications.

Potential conflicts of interest

The authors declare no conflicts of interest.

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