CLINICAL VIGNETTE

Adverse Cutaneous Reactions to Hydroxychloroquine: A Well-Documented, but often Forgotten, Clinical Phenomenon in Dermatomyositis

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Clinical Case

A 57-year-old woman with history of Hashimoto's thyroiditis, Hereditary hemochromatosis and Rheumatoid Arthritis presented to the rheumatology for a second opinion evaluation of her RA. Her RA diagnosis was made by an outside rheumatologist approximately 20 years prior and was being treated with Tofacitinib 11mg daily. She felt there was no benefit from the medication on her symptoms, which included persistent morning stiffness and pain in the MCP, PIPs, wrists, shoulders, and knees with intermittent swelling in the MCP and PIP joints. Historically, her symptoms were moderately responsive to non-steroidal anti-inflammatory drugs and various doses of corticosteroid therapy. However, she had tried and failed multiple steroid-sparing disease modifying anti-rheumatic drugs and biologics including: Sarilumab, Adalimumab, Etanercept, Methotrexate, and Abatacept. She had a sulfa allergy and was unable to trial sulfasalazine.

Physical exam was significant for tenderness of the bilateral PIP, MCP, wrist and MTP joints with mild swelling of the wrists and PIP joints of both hands. Radiographic evaluation including x-rays of the bilateral hands, wrists, shoulders, knees, ankles and feet showed no changes indicative of inflammatory arthritis or crystalline arthropathy. Serologic testing was significant for high titer Anti-nuclear antibody 1:1280, homogenous and speckled pattern. Rheumatoid factor and Anti-CCP antibodies were negative, as well as Anti SSA/SSB, Smith, RNP, dsDNA, Scl-70, Centromere, and histone antibodies.

Due to lack of efficacy, the patient discontinued Tofacitinib and had started a prednisone taper at 15mg daily with improvement of her symptoms. She was then started on Hydroxychloroquine 300mg daily for treatment. Two weeks after beginning Hydroxychloroquine, the patient developed severe, morbilliform dermatitis over >90% body surface area on the trunk and extremities. The dermatitis was pruritic and burning. Desquamation of the palms and soles was present. Complete blood count and complete metabolic panel were normal, and DRESS was ruled out. The patient was treated with oral corticosteroids and antihistamines with improvement of the acute rash but with persistent burning sensation and erythema of sun exposed areas: particularly the scalp. She was observed to have erythema in a V distribution on the chest, neck, torso as well as waxing and waning facial erythema.

Skin biopsy of the V shaped rash was non-specific, showing superficial, mid-dermal, perivascular chronic inflammation, suspicious for drug eruption. Further serologic testing demonstrated the presence of Nuclear matrix Protein -2 and TIF-1 gamma Antibodies. Creatine Kinase and Aldolase levels were normal. Patient was diagnosed with dermatomyositis. Investigation for occult malignancy was negative. She was unable to tolerate mycophenolate mofetil or azathioprine due to gastrointestinal side effects. She was started on weekly IVIG infusions with oral corticosteroid taper, and her cutaneous symptoms gradually improved over the next 5 months, at which time IVIG was discontinued due to severe headaches.

Discussion

Dermatomyositis is a rare, idiopathic systemic autoimmune disease with clinical manifestations mainly consisting of inflammatory myositis and characteristic cutaneous lesions including Gottron's papules, heliotrope rash, shawl sign, V sign, holster sign, cuticle overgrowth, and pruritic scalp, amongst others. Raynaud's syndrome and pulmonary disease, particularly interstitial lung disease, are other common manifestations. Diagnosis of Dermatomyositis is made based on clinical presentation but can be difficult when there is an absence of classic cutaneous symptoms, or when cutaneous symptoms are subtle and there is lack of myositis. In these cases, Myositis Specific Antibodies may be of utility in honing-in on the diagnosis earlier and screening for disease progression. Myositis specific antibodies are associated with specific disease phenotypes:[1]

Antibody	Phenotype	Clinical Features
Anti Jo-1	Anti- Synthetase Syndrome	Mechanics hands, Interstitial lung disease, Raynaud's, arthritis
Anti- Mi-2	Classic Dermatomyositis	Gottron's papules, Heliotrope rash, lung-sparing, steroid responsive
Anti-TIF1-gamma	Cancer-associated (Adults) Juvenile Dermatomyositis	Aggressive skin lesion (both adult and juvenile)
Anti-NXP-2	Cancer-associated (Adults) Juvenile Dermatomyositis	Severe cutaneous lesions, calcinosis (juvenile)
Anti-MDA5	Clinically Amyopathic	Reverse Gottron's, Rapidly progressive interstitial lung disease
Anti-SAE	Initially Amyopathic	Severe skin disease, dysphagia
Anti SRP	Necrotizing Myopathy	Severe, rapidly progressive and difficult to treat necrotizing myopathy
Anti-HMG Co A Reductase	Statin-induced Necrotizing	Necrotizing myopathy related to statin exposure

Choice of immunomodulating therapy for dermatomyositis is dependent on the severity of organ system involvement. Therapies may include methotrexate, azathioprine, mycophenolate mofetil, cyclophosphamide, rituximab, IV Immunoglobulin, and systemic corticosteroids in management of acute disease.

While hydroxychloroquine has been utilized as adjunct therapy to improve the cutaneous symptoms of dermatomyositis, there have also been well-documented cases of cutaneous reactions to hydroxychloroquine. A retrospective review of 532 patients with cutaneous lupus erythematosus (70%) and dermatomyositis (30%) revealed that the most common toxicities seen with antimalarial medications in these disease categories were cutaneous. Compared to hydroxychloroquine monotherapy, the risk of cutaneous eruption was significantly lower when hydroxychloroquine and quinacrine were co-administered (HR 0.231, 95% CI (0.07-0.82, p=0.0056). However, this analysis did not separate cutaneous lupus from dermatomyositis for subgroup analysis.[2]

Another study of 42 patients with dermatomyositis compared age-sex matched controls with Systemic Lupus erythematosus. Twelve (31%) of the dermatomyositis patients developed adverse cutaneous reaction to hydroxychloroquine as opposed to only one with Systemic Lupus Erythematosus. Eleven of these eruptions were morbilliform and started within three weeks of hydroxychloroquine initiation. Each resolved with discontinuation of hydroxychloroquine and most were treated with oral courses of prednisone.[3] In a cohort study of 111 patients with dermatomyositis treated with hydroxychloroquine, 23 experienced an adverse cutaneous event. This analysis found skin eruptions were approximately three times more common in patients with anti-SAE antibodies, and that the presence of anti-MDA5 antibodies was significantly negatively associated with hydroxychloroquine associated skin eruption. Hydroxychloroquine associated drug eruptions were seen in the presence of Anti-TIf-1gamma and Anti-NXP-2 antibodies (the antibodies our patient had), but there was no significant association between these antibodies and the occurrence of drug eruption.[4]

Sanches et al reported a 70-year-old woman with an initial diagnosis of cutaneous lupus who developed a severe, morbilliform reaction after two weeks of hydroxychloroquine therapy. The rash improved with oral prednisone administration and discontinuation of hydroxychloroquine. In subsequent months, she developed mechanics hands, heliotrope sign, and photosensitive V—sign and was found to have positive Anti-SAE1/2 antibodies and was diagnosed with Dermatomyositis.[5] This is similar to our patient, who had been previously diagnosed with another systemic autoimmune disease, Rheumatoid Arthritis, and subsequently developed a severe cutaneous reaction with Hydroxychloroquine therapy. Like Sanches et al, our case emphasizes the importance of a history of drug eruption to hydroxychloroquine for suspecting the diagnosis of dermatomyositis.

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