Dermatomyositis-like Rash Associated with Anti-3-hydroxy-3-methylglutaryl-coenzyme A Reductase Autoantibody Necrotizing Myopathy Following COVID-19 Infection and Vaccination

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Introduction

The clinical presentation of immune-mediated necrotizing myopathies (IMNM) includes the acute or subacute onset of severe, symmetric proximal weakness with potential for facial weakness and/or dysphagia, elevated creatinine kinase (CK), predominant myofiber necrosis with minimal inflammation on muscle biopsy, and minimal or no extramuscular manifestations. [1-3] Recently, there have been rare case reports of patients presenting with a characteristic dermatomyositis (DM)-type rash, including a heliotrope rash or Gottron's papules, who were subsequently found to have serologic evidence of 3-hydroxy-3-methylglutaryl-coenzyme A reductase (HMGCR) antibodies and muscle biopsies most consistent with IMNM as opposed to perifascicular atrophy and predominant perivascular perimysial inflammation.[2,4-6] Here we present an additional case of a 62-year-old female who presented with a characteristic heliotrope and bimalar rash who was subsequently found to have HMGCR-associated necrotizing myopathy temporally associated with her 2nd mRNA COVID-19 vaccination and remote history of statin exposure.

Case Report

A 62-year-old female with a history of diabetes mellitus type II and hypertension presented for consultation regarding 3 months of progressive weakness in her bilateral upper and lower extremities. She reported a history of a mild SARS-CoV-2 infection 10 months prior to initial consultation during which she noted diffuse muscle aches and difficulty standing for long periods of time for a 3-week period, however, returned to her baseline level of function following recovery. She did not require any hospitalization.

She first noted recurrence of her muscle aches and difficulties standing for prolonged periods of time approximately 2 weeks following her second mRNA COVID-19 vaccination 3 months prior to consultation. As opposed to her prior SARS-CoV-2 infection experience, the onset of her symptoms was more subacute per the patient's report, and she initially attributed them to side effects from her vaccination. Unfortunately, the patient's symptoms failed to improve over the subsequent 3 weeks and she began to notice difficulty getting in and out of a chair without using her hands. She could not brush her hair without resting and needed to rest her arm against the shower wall in order to wash her hair. Symptoms continued to progress to the point where she required assistance from two people to stand up out of a vehicle and could no longer walk without the use of a cane for short distances and required a wheelchair when out of the home. She denied any swallowing difficulties but did notice some dyspnea with exertion. She denied any diplopia or sensory changes. She noticed a new-onset bimalar erythematous rash one month prior to consultation but denied any rash on her trunk or hands.

Given the progressive weakness, she was initially referred to an outside neurologist who obtained an EMG which demonstrated myopathic findings with membrane irritability in the right deltoid, biceps, triceps, flexor carpi radialis, vastus medialis, and iliopsoas, consistent with a myopathy with muscle membrane irritability, as well as a mild to moderate axonal sensorimotor polyneuropathy based on absent sural and superficial peroneal sensory responses and borderline low or low peroneal and tibial motor study amplitudes. Imaging obtained included a cervical spine MRI which was within normal limits, brain MRI which demonstrated some mild age-related involutional changes but was otherwise unremarkable, and lumbar spine MRI which demonstrated facet hypertrophy with moderate central canal narrowing and moderate to severe left L5-S1 neuroforaminal stenosis. Her CK was found to be elevated at 6,892 U/L and she was referred to the neuromuscular clinic for further evaluation.

Initial examination 2 weeks after her initial outside neurology consultation demonstrated mild neck flexor (MRC 4/5) and extensor (4+/5) weakness with proximal weakness noted in the shoulder abductors (4-/5), shoulder external rotation (4/5), and forearm pronation (4/5) bilaterally. Elbow flexion was 4+/5 bilaterally. Lower extremity strength demonstrated moderate hip flexion weakness (3-/5) and hip abduction/adduction weakness (4-/5) bilaterally with mild knee extension/flexion (4/5) weakness and preserved ankle dorsiflexion/plantarflexion. Sensation was grossly intact to pinprick without a length-dependent gradient with some vibratory loss in the left

lower extremity at the ankle attributed to local edema. Reflexes were preserved (2/4) with the exception of the Achilles' reflexes (0/4) and the patient had a waddling gait which required the assistance of a single point cane. She was noted to have a bimalar erythematous rash (Figure 1) but no other skin abnormalities. She was not currently taking statin medications but noted she was on atorvastatin for 1 month (stopped due to myalgias) over 5 years prior to presentation.

Given her presentation, the patient was referred for a left biceps muscle biopsy the following day which demonstrated mild fiber size variability with predominant necrosis and regeneration without perifascicular changes or predominant perivascular perimysial inflammation most consistent with a necrotizing myopathy (Figure 1). Laboratory results which returned following the results of the biopsy demonstrated an elevated HMGCR antibody of greater than 200 units (normal 0-19). A myositis-specific antibody panel demonstrated negative Jo-1, PL-7, PL-12, EJ, OJ, SRP Mi-2, U3 RNP, MDA-5, NXP-2, TIF-1 Gamma, Anti-PM/Scl-100, US snRNP, U1-RNP, KU, SSA, SSB, and SAE antibodies. Her ANA titer was positive at 1:320.

Malignancy screening including CT of the chest, abdomen, and pelvis, mammogram, and serum immunofixation and kappa/lambda light chain ratios was negative except for likely reactive pelvic lymph nodes with recommendation for repeat pelvic CT in 3-4 months. The patient was started on a regimen of oral prednisone as well as weekly oral methotrexate and has noted some functional improvements despite only being on therapy for 3 weeks. She has also noted improved swelling around her orbits but continues to note some erythema. Given her temporal course related to her mRNA COVID-19 vaccination, she has also been referred for enrollment in an NIH study evaluating the association of myositis with COVID-19 vaccines.

Discussion

Immune-mediated necrotizing myopathies account for approximately 20% of autoimmune myopathies with anti-HMGCR antibodies representing the most frequently associated antibody, ranging from 22 to 61% of cases, with anti-SRP representing the next most frequently associated autoantibody.[1,3,7] The frequency of anti-HMGCR antibodies is highest in older patients with prior statin exposure. However, since its discovery in 2010 it has been associated with statin naïve patients as well as those with an underlying malignancy.[1,8,9] In addition, while rare, anti-

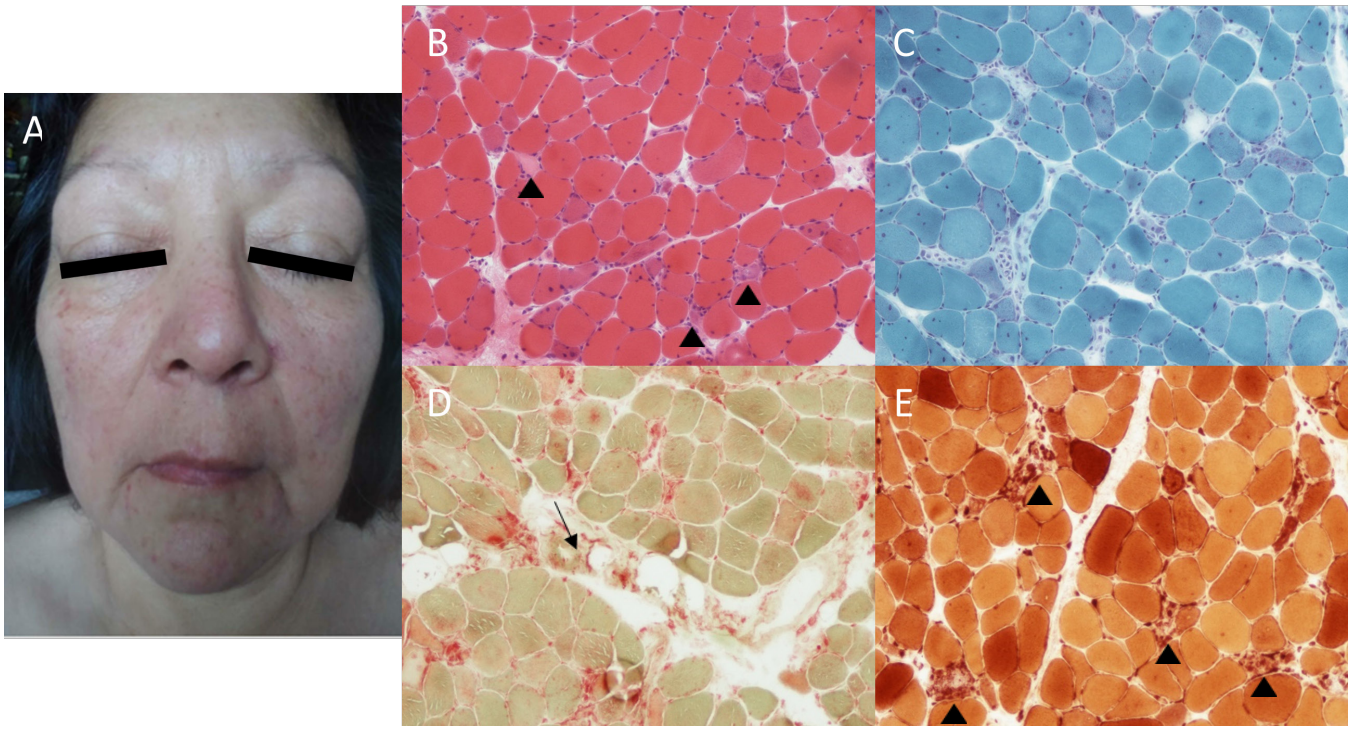

Figure 1. Erythematous heliotrope and bimalar rash (A) noted on initial examination. Left biceps muscle biopsy. H&E (B) and Gomori Trichrome (C): mild fiber size variability with many necrotic fibers and several undergoing myophagocytosis (arrowheads) with scant inflammation. Acid Phosphatase (D) with many necrotic fibers and a single focus of perivascular inflammation (arrow). Non-specific esterase (E) with several fibers undergoing myophagocytosis (arrowheads). No perifascicular atrophy or prominent perivascular perimysial inflammation was noted on any of the stains.

HMGCR antibodies have been reported in other idiopathic inflammatory myopathies (IIM) and connective tissue diseases, including 1.9% of adult-onset DM cases, 6.7% of juvenile DM cases, and 1.2% of primary Sjögren's syndrome cases.[2,9-11]

The typical presentation of IMNM associated with anti-HMGCR antibodies is associated with a mean age of onset of 55 with a female predominance of acute to subacute onset of progressive proximal extremity weakness, more pronounced in the lower extremities. CK is elevated at least 10 times the upper limit of normal and remains elevated despite stopping statin therapy if the patient was previously exposed.[1,3,7] Typical biopsy findings include predominant myofiber necrosis with myophagocytosis and regeneration with scant inflammation. MAC and MHC-1 expression on the sarcolemma of non-necrotic fibers as well as MAC deposition on small blood vessels has also been described.[1,3,12] While bulbar and respiratory involvement is rare, some case series have noted dysphagia.[1,7,8]

Skin involvement has been noted in 15-44% of anti-HMGCR-positive patients, however, specific findings for dermatomyositis such as Gottron's papules, Gottron's sign, or heliotrope rash, were uncommon.[7,12-15] To our knowledge, there are only four additional case reports of biopsy proven statin-associated anti-HMGCR with a specific DM skin rash (i.e. Gottron's papules, Gottron's sign, or heliotrope rash).[2,4-6,10] This clinical entity has been recognized in the most recent 2018 ENMC dermatomyositis classification criteria as "anti-HMGCR myopathy with a DM-like rash" with a single case series comparing these patients against those with HMGCR antibodies without a DM-like rash and noting those with DM-like rashes had a younger age of onset and shorter disease duration at time of diagnosis.[13,16]

In addition to the unique skin findings, the significance of the temporal relation to the patient's second COVID-19 vaccination and her prior COVID-19 infection remains uncertain. While the most common presentation of the SARS-CoV-2 infection includes fever and upper and lower respiratory symptoms, generalized myalgias have been seen in up to 50% of cases.[17,18] Progression to myopathy or myositis has only been rarely reported with only a few case reports of rhabdomyolysis which was acute and concurrent with SARS-CoV-2-related pneumonia as well as flaccid quadriplegia after intensive care management.[19-21] While necrotizing autoimmune myopathy is typically idiopathic, triggers outside of statin exposure or underlying malignancy also may include post-viral autoimmune antibodies.[22] There is a single case report of SARS-CoV-2 IgG positive autoimmune necrotizing myopathy with negative HMGCR and SRP antibodies one month following an initial COVID-19 infection which responded to immunotherapy.[19] To date there have been no clear cases of autoimmune myopathy related to COVID-19 vaccination with only a single case report of a self-limited vaccine related myositis which resolved spontaneously 6 weeks after onset of symptoms without intervention.[23]

Anti-HMGCR myopathy with a DM-like rash appears to be a unique clinical entity with a younger age of onset and shorter duration of symptoms as compared to HMGCR antibody-positive IMNM without typical DM-like skin manifestations. This case outlines the importance of muscle biopsy and complete serologic testing for myositis-associated antibodies in securing the correct diagnosis, even in the setting of specific skin manifestations for dermatomyositis. As anti-HMGCR antibodies are not on routine myositis panels, these antibodies should be considered in addition to routine myositis-specific antibodies in those patients with a significant CK elevation with or without prior statin exposure even in the setting of a DM-like rash, as this may have therapy implications given the often-inadequate response to corticosteroid monotherapy in IMNM. Finally, while we cannot rule out a causal relationship between onset of her HMGCR-positive IMNM and her COVID-19 infection and/or vaccination, this relationship will require further exploration by means of enrollment in larger patient databases to better understand whether there is a true relationship between COVID-19 vaccination and/or infection and subsequent development of IMNM or other IIM.

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