

# Statin-naïve anti-3-hydroxy-3-methylglutaryl coenzyme A reductase antibody-positive necrotizing myopathy with heliotropic pseudoangioedema



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## INTRODUCTION

Immune-mediated necrotizing myopathies (IMNMs) are a group of inflammatory myopathies that present with significant morbidity and mortality, marked by severe muscle necrosis; a highly elevated serum creatine kinase (CK) level; and risk of long-term muscle impairment. This disease class resembles polymyositis and was only made distinct in 2004, with subsequent identification of autoantibodies against 3-hydroxy-3-methylglutaryl coenzyme A reductase (HMGCR) in 2010.<sup>1</sup> IMNMs are mostly associated with specific autoantibodies to HMGCR and the signal recognition particle and are further subclassified as anti-HMGCR antibody-positive, anti-signal recognition particle antibody-positive, and seronegative IMNM. Although anti-HMGCR antibody-positive cases are usually associated with statin use, about one third of the cases are statin-naïve, some of which, have been linked to red yeast rice and oyster mushroom consumption which are natural sources of a lovastatin analog.<sup>2</sup> The patients in this subset of cases are typically younger, have a more severe presentation, and are more likely to develop a refractory, chronic course.<sup>3</sup> Although the medical community has only recently begun characterizing this condition, it classically does not display extramuscular involvement or specific cutaneous manifestations.<sup>4</sup> Here, we report an interesting case of a young patient with biopsy-confirmed anti-HMGCR antibody-positive IMNM, who

### Abbreviations used:

CK:	creatine kinase
DM:	dermatomyositis
HMGCR:	3-hydroxy-3-methylglutaryl coenzyme A reductase
IMNM:	immune-mediated necrotizing myopathy

presented with heliotropic pseudoangioedema and other skin manifestations.

## CASE REPORT

A 20-year-old female college wrestler with an 11-month history of statin-naïve anti-HMGCR antibody-positive IMNM and no known exposure to red yeast rice or oyster mushrooms presented to our dermatology clinic in July 2021 with an edematous, violaceous plaque on her right forearm, bilateral edematous heliotrope rash, and a subtle, ill-defined violaceous patch on her chest. One year previously, she was admitted to an outside hospital for worsening muscle pain, weakness, weight loss, and an elevated CK (15,912) level. Skin examination revealed a heliotrope rash and erythematous pruritic patches involving her chest, neck, and upper arms. Laboratory findings were notable for aspartate aminotransferase (1,325), alanine aminotransferase (583), aldolase (205.8), erythrocyte sedimentation rate (111), and C-reactive protein (315). Tests for antinuclear antibodies and a classic myositis panel

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(eg, anti—signal recognition particle, anti—Jo-1, and anti—Mi-2) were negative, and a pan computed tomography did not reveal any sign of malignancy. Her CK level up-trended to 30,420, at which point a muscle biopsy specimen of the right quadriceps revealed scattered, degenerated muscle fibers with no inflammatory infiltrate.

Anti-HMGCR autoantibody serology was strongly positive (504). Normal breast and thyroid ultrasounds, cancer antigen tests (CA-19/CA-125), and a blood smear ruled out occult malignancy. Magnetic resonance imaging of her pelvis revealed diffuse T2 hyperintensities of the pelvic muscles. She was diagnosed with anti-HMGCR antibody-positive IMNM and prescribed azathioprine 150 mg daily, prednisone 60 mg daily, and 2 rituximab infusions. She showed gradual clinical improvement and was discharged on a prednisone taper, azathioprine, and monthly intravenous immunoglobulin, which were weaned over the subsequent 3 months.

She presented to an outside hospital 6 months later for flare of her disease. She was prescribed hydroxychloroquine and scheduled for intravenous immunoglobulin. After failed peripheral line placement, she developed a rash near the injection site on the right arm and was referred to our dermatology clinic for evaluation. Physical examination revealed erythema and edema on the upper and lower eyelids of both of her eyes (Fig 1). On her chest, an ill-defined, violaceous, slightly poikilodermatous patch was observed (Fig 2). Along the right forearm, near the failed infusion site, there was a blanching, edematous, violaceous patch that was warm and tender to palpation (Fig 3). Suspecting a thrombotic complication, she was sent to the emergency department for workup, where they ruled out superficial and deep venous thrombosis with Doppler ultrasound and discharged her with rheumatology follow-up.

## DISCUSSION

In the literature, statin-naïve anti-HMGCR antibody-positive IMNM is traditionally thought to lack skin manifestations; for this reason, we present a case of statin-naïve anti-HMGCR antibody-positive IMNM with heliotropic pseudoangioedema. We believe that dermatologists should be made aware of this condition's variable cutaneous presentation to differentiate it from dermatomyositis (DM) and avoid delays in effective management.

Like DM, statin-naïve anti-HMGCR antibody-positive IMNM is characterized by symmetrical proximal muscle weakness and myalgia. However, it distinguishes itself via a remarkably elevated CK level, rapidly progressing weakness, and stronger association with dysphagia, dysarthria, and



**Fig 1.** Erythema and edema mimicking the heliotrope rash of dermatomyositis on the upper and lower eyelids of both eyes.



**Fig 2.** Slight poikilodermatous and violaceous macules on the upper, anterior aspect of the chest.

respiratory muscle weakness, particularly in younger individuals.<sup>3</sup> Although cutaneous findings are not classically described, there is a growing body of case reports suggesting associations with nondescript rashes.<sup>5</sup> One case series found that 9 of 21 anti-HMGCR antibody-positive patients had DM-like rashes, including heliotrope rash, Gottron sign, and erythema of the cheeks, limbs, chest, abdomen, and back; these patients were more likely to be younger and to experience juvenile-onset disease compared with anti-HMGCR antibody-positive patients without DM-like rashes.<sup>6</sup>

Interestingly, Xu et al<sup>7</sup> recently reported that pseudoangioedema, subcutaneous swelling resembling angioedema found in nonurticarial conditions such as drug rash with eosinophilia and systemic symptoms and acute contact dermatitis,<sup>8</sup> in patients with DM portends more severe disease and poorer prognosis. These patients exhibited nonpitting edema with no history of other edema-causing



**Fig 3.** Right forearm with a blanching violaceous and erythematous plaque that was warm and tender to palpation with associated edema.

diseases and nonpruritic rashes that failed to respond to antihistamines. The pseudoangioedema correlated temporally with the disease course of DM: onset/worsening during exacerbation and resolution after immunotherapy. Our patient similarly presented with a heliotrope rash and chest/arm skin eruption with pseudoangioedema in the setting of IMNM flare. Perhaps, pseudoangioedema may also act as a clinical clue in IMNM, suggesting risk of heightened severity and worse outcomes.

Important workup for distinction between pathologies includes muscle biopsy and serum antibody testing. Muscle biopsy in anti-HMGCR antibody-positive IMNM demonstrates necrosis with a pauc inflammatory infiltrate, whereas biopsy specimens of DM rarely show necrosis, instead displaying a perivascular and perifascicular CD4<sup>+</sup> T-lymphocytic infiltrate and perifascicular atrophy.<sup>6,9</sup> Both have a higher incidence of cancer, with DM showing a stronger association compared with anti-HMGCR antibody-positive IMNM (6-fold vs 2-fold increase).<sup>2</sup> Lastly, DM and anti-HMGCR antibody-positive IMNM differ in their treatments with the latter more often necessitating intravenous immunoglobulin, rituximab, and systemic corticosteroids, as required by our patient.<sup>10</sup>

In conclusion, this case highlights the presentation of a rare disease with significant morbidity risk that may cause confusion with DM because of its heliotropic pseudoangioedematous presentation. As we are now beginning to better characterize IMNM, this case contributes to the medical community's understanding of variations in its presentation, particularly among younger patients. Because statin-naïve anti-HMGCR antibody-positive necrotizing myopathy is one of the most severe inflammatory myopathies, we share our observations in the hope that they may lead to earlier diagnosis and timely escalation of immunotherapy. Further investigation is required to better elucidate the pathophysiology of this complex autoimmune disease and identify patients who are susceptible.

#### Conflicts of interest

None disclosed.

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