

# Ulcerative Heliotrope Rash in Antimelanoma Differentiation–Associated Gene 5 Dermatomyositis

T. Tyler Daugherty, MD; Justin T. Cheeley, MD

## PRACTICE POINTS

- Antimelanoma differentiation–associated gene 5 dermatomyositis (anti-MDA5 DM) can present with an ulcerative heliotrope rash.
- Ulceration of the heliotrope rash in anti-MDA5 DM may indicate disease progression.
- Rapidly progressive interstitial lung disease is highly associated with anti-MDA5 DM.

Antimelanoma differentiation–associated gene 5 dermatomyositis (anti-MDA5 DM) is an amyopathic subtype of DM that presents with the classic cutaneous findings of DM, such as a heliotrope rash, Gottron papules, and the shawl sign, combined with mucocutaneous ulcerations. This subtype of DM also is highly associated with rapidly progressive interstitial lung disease (ILD). We report 2 cases of a heretofore novel presentation of the overlap of these cutaneous features in the form of an ulcerative heliotrope rash; furthermore, the rash was associated with progression of ILD in both cases. Finally, we review the current state of clinical care and research related to anti-MDA5 DM in terms of clinical presentations, diagnostic methods, and treatment options.

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**D**ermatomyositis (DM) is an autoimmune condition characterized by skin and muscle inflammation with an estimated incidence of 9 cases per 1 million people. The incidence of amyopathic DM, which

includes antimelanoma differentiation–associated gene 5 (anti-MDA5) DM, is approximately 2 cases per 1 million people.<sup>1</sup> Classic cutaneous manifestations of DM include a heliotrope rash, Gottron papules, and the shawl sign. Features of anti-MDA5 DM include cutaneous ulcerations, most commonly overlying Gottron papules on the elbows and digits, as well as painful palmar macules and papules. We describe 2 patients with anti-MDA5 DM who presented with an ulcerative heliotrope rash. Although heliotrope rash is classic for DM and cutaneous ulcerations are a hallmark of the anti-MDA5 subtype of DM, overlap of these cutaneous manifestations is not commonly reported. Furthermore, ulcerations of the lateral canthi were associated with rapidly progressive interstitial lung disease (ILD).

## Case Reports

**Patient 1**—A woman in her 30s presented with diffuse arthralgias, bilateral eyelid edema, fatigue, and a progressive diffuse exanthem of 3 months' duration. A review of systems was notable for the absence of myalgias. Physical examination revealed periorbital poikilodermatous patches with erythematous-to-violaceous plaques along the eyelid margins, violaceous papules on the dorsal knuckles, and edematous eroded plaques on the palmar fingertips. The patient was found to have a positive antinuclear antibody titer of 1:320 (reference range, <1:80) with a speckled pattern. A computed tomography (CT) scan of the chest showed patchy bilateral ground-glass opacities that were concerning for ILD. The

From the Department of Dermatology, Emory University School of Medicine, Atlanta, Georgia. Dr. Cheeley also is from the Division of Internal Medicine and Geriatrics.

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Correspondence: Justin T. Cheeley, MD, 1525 Clifton Rd NE, Dermatology Office Ste 100, Office 122, Atlanta, GA 30322 (jcheele@emory.edu). doi:10.12788/cutis.0260

cutaneous erosions, absence of myalgias, considerable proximal weakness, radiographic evidence of ILD, and positive antinuclear antibody test were clinically suggestive of anti-MDA5 DM. Further workup confirmed this diagnosis with positive reactivity to MDA5 by line immunoassay. The patient was treated with intravenous corticosteroids and was discharged after a 17-day hospitalization; however, she presented 2 months later to outpatient dermatology for progression of the cutaneous ulcerations, at which time an ulcerative heliotrope rash (Figure 1) was identified. Despite compliance with oral corticosteroids (1 mg/kg/d), she was hospitalized 1 month later for progressive respiratory insufficiency. A chest CT showed ground-glass linear opacities centrally located in all lobes of both lungs, consistent with rapidly progressive ILD. Over the course of her 5-day hospitalization, she was treated with corticosteroids, intravenous immunoglobulin (IVIG), and mycophenolate mofetil. The patient responded well to these therapies, leading to resolution of the respiratory symptoms, and she was discharged with plans to continue this regimen as an outpatient.

**Patient 2**—A woman in her late 30s with a history of known anti-MDA5 DM confirmed by line immunoassay 1 year prior presented to the emergency department with shortness of breath due to progressive ILD and a worsening exanthem. Dermatology was consulted to provide treatment recommendations. The treatment team was concerned for infection or anti-MDA5 DM disease progression. Physical examination revealed an ulcerative heliotrope rash (Figure 2) in addition to cutaneous findings classic for anti-MDA5 DM. Despite interventions,

including high-dose corticosteroids, rituximab, IVIG, and plasma exchange, the ILD continued to progress, and the patient and her family elected to de-escalate aggressive medical care and pursue comfort care. The patient later died in inpatient hospice.

**Comment**

*Clinical Presentation of Anti-MDA5 DM*—Dermatomyositis classically presents with cutaneous manifestations including a heliotropic erythematous rash and Gottron papules as well as accompanying muscle weakness.<sup>2</sup> However, a subtype known as amyopathic DM, which includes anti-MDA5 DM, usually presents without muscle involvement.<sup>3</sup> Clinical muscle weakness has been reported in cases of anti-MDA5 DM, though it is less likely in these patients.<sup>4</sup> The characteristic cutaneous phenotype of anti-MDA5 DM was described by Fiorentino et al<sup>5</sup> in 2011 through a seminal retrospective study. Kurtzman and Vleugels<sup>6</sup> provided validation of the clinical features of anti-MDA5 DM in their 2018 review. The classic cutaneous phenotype of anti-MDA5 DM consists of tender palmar papules and/or skin ulcerations that commonly develop over Gottron papules on the knuckles and digits, lateral nail folds, and elbows.<sup>7-10</sup> A meta-analysis of 1500 patients with anti-MDA5 DM found a statistically significant association with alopecia, Gottron sign or papules, mechanic’s hands, and V rash ( $P < .05$ ), as well as skin ulcers, panniculitis, arthritis/arthritis, pneumomediastinum, and rapidly progressive ILD (RP-ILD) ( $P \leq .01$ ).<sup>4</sup> Rapidly progressive ILD is highly associated with anti-MDA5 DM.<sup>6,11</sup>

While a heliotrope rash is classic for DM, and ulcerations are a hallmark of the anti-MDA5 DM subtype, overlap of these cutaneous manifestations is not commonly reported. In both cases presented here, ulcerations of the lateral canthi were associated with progression of ILD.



**FIGURE 1.** Ulcerative heliotrope rash in antimelanoma differentiation-associated gene 5 dermatomyositis. Punched-out-appearing ulcer of the left lateral canthus.



**FIGURE 2.** Ulcerative heliotrope rash in antimelanoma differentiation-associated gene 5 dermatomyositis. Heme-crusting ulcer of the left lateral canthus.

**Diagnosis of Anti-MDA5 DM**—Anti-MDA5 DM is defined by the presence of the anti-MDA5 antibody in the serum, named for its reactivity against the RNA helicase encoded by MDA5, within the clinical context of cutaneous signs of DM as described above.<sup>12</sup>

As described by Rider et al,<sup>13</sup> a thorough laboratory analysis, including complete blood cell count, serum electrolytes, calcium, magnesium, phosphorus, and thyroid-stimulating hormone, is necessary to rule out conditions with similar presentations. Additionally, serum analysis for elevated muscle enzymes (creatinine phosphokinase, aldolase, lactate dehydrogenase, alanine aminotransferase, and aspartate aminotransferase) is necessary to assess for subclinical muscle involvement. Serologic evidence of myositis usually denotes an alternative diagnosis.<sup>13</sup> Antinuclear antibodies and myositis-specific antibody positivity are much less frequent in the anti-MDA5 DM subtype than in other forms of DM.<sup>6</sup>

Anti-MDA5 antibody titer, ferritin, and IL-18 can be trended and may be useful in the evaluation of the response to treatment and ILD status in patients with anti-MDA5 DM.<sup>14,15</sup> Elevated alveolar-arterial gradient, serum ferritin, serum chitotriosidase, and serum chitinase-3-like protein 1 (YKL-40) have each been associated with poorer prognosis of anti-MDA5 DM. The aforementioned serologies therefore may be helpful in determination of risk stratification and treatment aggressiveness.<sup>16-19</sup>

Because of its strong association with RP-ILD, screening for pulmonary disease is necessary in all patients with confirmed or strongly suspected anti-MDA5 DM. Screening can be performed with pulmonary function testing; however, high-resolution chest CT is the gold standard for diagnosis of ILD.<sup>20</sup>

Finally, all patients with a new diagnosis of DM should be evaluated for underlying malignancy through cancer screenings, given the propensity for DM to present as a paraneoplastic process.<sup>21</sup> However, reports have indicated that the anti-MDA5 DM subtype may have a reduced risk for or an inverse relationship with underlying malignancy.<sup>5</sup>

**Treatment Options for Anti-MDA5 DM**—Early and aggressive therapy should be considered in the treatment of anti-MDA5 DM because of its association with RP-ILD. No treatment protocol is well established; thus, an individualized therapeutic approach may be guided by symptom severity and the clinical, radiographic, or functional evidence of ILD.<sup>6</sup> High-dose systemic corticosteroids are first line, either in combination with or as a bridge to corticosteroid-sparing agents for immunosuppression. Many steroid-sparing medications have been employed with varying success. Mycophenolate mofetil is a reasonable first-line corticosteroid-sparing immunosuppressant agent, given its added benefit of attenuating ILD progression.<sup>6</sup> A combination of high-dose corticosteroids, cyclosporine, and cyclophosphamide is utilized by some initially in the treatment of anti-MDA5 with

ILD.<sup>22,23</sup> While others have used combinations of these immunomodulatory agents with mycophenolate mofetil, IVIG, rituximab, azathioprine, tofacitinib, and polymyxin B, direct hemoperfusion has been added, leading to successful remission.<sup>23-28</sup>

## Conclusion

We present 2 patients with anti-MDA5 DM who demonstrated a rare cutaneous manifestation of an ulcerative heliotrope rash. In both cases, this cutaneous finding was associated with the development of RP-ILD. Because of the strong association with and rapid progression of ILD seen in anti-MDA5 DM, early identification and aggressive treatment of this subtype are imperative. The clinician should recognize nonacral locations of cutaneous ulcerations, including an ulcerated heliotrope rash, to optimize diagnosis and management.

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