CLINICAL PRACTICE
Clinical Vignettes

Anti-MDA5 Antibody-Associated Clinically Amyopathic Dermatomyositis: Case Report and Literature Review

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INTRODUCTION

Idiopathic inflammatory myopathies (IIMs) encompass a group of heterogeneous diseases that often involve multiple organ systems and sometimes have minimal to no effect on muscle tissue. IIMs were classically described according to their clinical and histological findings as polymyositis, dermatomyositis, and inclusion body myositis. Today, IIMs are increasingly categorized according to a number of myositis-specific antibodies (MSAs) discovered over the last several years that are each associated with distinct clinical syndromes. The auto-antibody against the melanoma differentiation-associated protein 5, or anti-MDA5 antibody, is a recently recognized MSA associated with a distinct clinical syndrome that includes the rapid progression of interstitial lung disease (ILD) and skin findings of dermatomyositis, but with little to no evidence of myositis (known as clinically amyopathic dermatomyositis). We present a case of anti-MDA5 antibody-associated clinically amyopathic dermatomyositis with rapidly progressive ILD in order to emphasize the importance of obtaining a complete history of present illness and performing a thorough physical exam, illustrate the wide spectrum of clinical findings associated with IIMs, raise awareness of anti-MDA5 antibody-associated clinically amyopathic dermatomyositis, and highlight the importance of MSAs in the diagnosis and management of IIMs.

CASE

A 44-year-old man with a history of gastroesophageal reflux disease and longstanding Raynaud's syndrome presented to the emergency department for three days of acutely worsening dyspnea following the development of chronic progressive dyspnea over the last nine months. Prior to the onset of symptoms nine months ago, the patient was generally healthy and had no notable shortness of breath or limitation in his exercise tolerance. As his symptoms progressed, he became dyspneic with minimal exertion and ultimately developed conversational dyspnea at rest. He also developed a dry cough. During the preceding two months, the patient noted a new red rash that appeared across his face, chest, back, elbows, and hands. The rash was not pruritic, though the elbow lesions were painful. He noted diffuse weakness in his arms and legs and was unable to walk across the room. He experienced two months of progressive dysphagia with recurrent aspiration multiple times per week. Review of systems also was notable for oral ulcers, alopecia, arthralgias without synovitis, and unintentional weight loss of 50 pounds. He denied orthopnea, lower extremity edema, chest pain, palpitations, and sicca symptoms.

He was admitted for dyspnea four times in the five months prior to hospitalization at our facility. Each time he was diagnosed with pneumonia without an infectious etiology identified and treated with antibiotics, which did not improve his symptoms. Three weeks prior to the most recent admission at our facility, the patient was admitted to another hospital for hypoxemic respiratory failure. A transthoracic echocardiogram revealed normal cardiac function. Serologic testing for antineutrophil cytoplasmic antibodies, antinuclear antibodies, human immunodeficiency virus, anti-cyclic citrullinated peptide antibodies, and anti-Scl-70 antibodies were negative. A bronchoscopy was performed and the bronchoalveolar lavage revealed a cell count of 147 cells/μL with 69% neutrophils; gram stain and culture for bacterial and fungal pathogens and staining for *Pneumocystis jirovecii* were negative. He received prednisone 40 mg daily in addition to antibiotics for presumed pneumonia and his condition improved. The patient was discharged and completed a 5-day course of prednisone at home; shortly thereafter, he experienced dyspnea at rest and presented to our emergency department.

On admission to the intensive care unit, the patient was afebrile, normotensive, tachycardic to 120 beats per minute, and tachypneic to 32 respirations per minute. He required high-flow nasal oxygen (HFNO) at 40 liters per minute (Lpm) and a fraction of inspired oxygen (FiO_2) of 50% to maintain pulse oximetry readings of 92%. The patient was in mild respiratory distress but was able to speak in short

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sentences with HFNO. Cardiovascular exam revealed tachycardia, but was otherwise normal. Other than tachypnea, his pulmonary exam was normal. Periorbital edema without hyperpigmentation was present as well as diffuse facial erythema and significant alopecia. His skin was notable for a V-shaped confluence of multiple violaceous, blanchable patches across his chest, neck, and shoulders. He had periungual erythema, violaceous macules across the dorsum of his hands, as well as erythematous hyperkeratotic plaques with 1-cm ulcers on his bilateral elbows (Images 1 and 2). His right fifth proximal interphalangeal joint was tender to palpation without swelling; the left second and third metacarpophalangeal joints were swollen, but nontender to palpation. Strength was normal in all proximal and distal muscle groups, but was unable to stand from bed due to respiratory distress.

Arterial blood gas analysis showed a pH of 7.48, pCO_2 of 36 mmHg, pO_2 of 84 mmHg, and HCO_3 of 21 mEq/L on HFNO at a FiO_2 of 50%. A complete blood count with differential, basic metabolic panel, urinalysis, and creatine kinase (CK) were normal. A C-reactive protein was elevated at 33 mg/L. A chest radiograph showed diffuse bilateral opacities. A subsequent high-resolution CT scan of the chest revealed extensive ground-glass opacities with septal thickening in a "crazy paving" pattern throughout the left lung and scattered in the right lung, concerning for ILD (Image 3). Given his recent hospitalization and critical illness, he was started on vancomycin and cefepime as treatment for possible hospital-acquired bacterial pneumonia.

An infectious work-up included a nasopharyngeal swab for severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), blood cultures, and legionella, cryptococcus, coccidioides, and histoplasma antigens, which were all negative. The dermatologic findings suggestive of dermatomyositis, rapidly progressive ILD, and the absence of muscle weakness on exam created a limited differential diagnosis including some forms of anti-synthetase syndrome and anti-MDA5 antibody-associated clinically amyopathic dermatomyositis. This limited differential led to serologic testing for a variety of MSAs as part of a panel of tests for IIMs. The patient tested strongly positive for the anti-MDA5 antibody and was subsequently

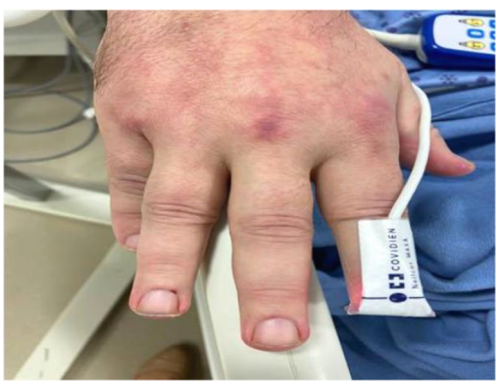

Image 1 Admission physical exam notable for periungal erythema and violaceous macules across the dorsum of his hands.

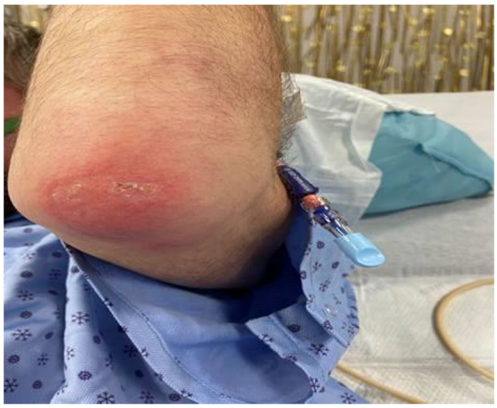

Image 2 Admission physical exam notable for erythematous hyperkeratotic plaques with 1-cm ulcers on his bilateral elbows.

diagnosed with anti-MDA5 antibody-associated clinically amyopathic dermatomyositis. He was treated with high-dose corticosteroids, cyclophosphamide, and tacrolimus for immunosuppression, as well as valganciclovir and trimethoprim/sulfamethoxazole for prophylaxis against opportunistic viral and bacterial pathogens, respectively. The patient's hypoxemia gradually improved with this treatment and he was discharged one month later on 2 L of supplemental oxygen. Over the next several months, the patient required recurrent hospitalization for worsening hypoxemia due to disease progression, but his condition stabilized following treatment with plasmapheresis and rituximab therapy. At the time of this writing, his clinical status remains tenuous.

DISCUSSION

This case highlights the presentation of a rare and often misdiagnosed disease, anti-MDA5 antibody-associated clinically amyopathic dermatomyositis. Of the IIMs, the diagnosis of

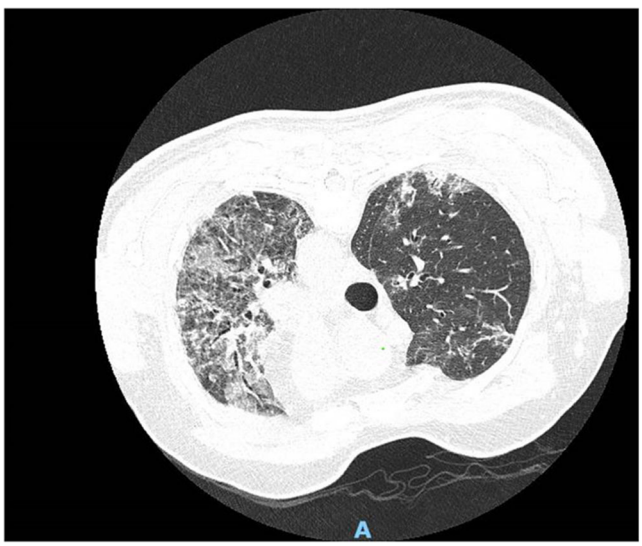

Image 3 High-resolution CT scan of the chest revealed extensive crazy paving throughout the left lung and scattered throughout the right lung, concerning for ILD.

amyopathic dermatomyositis may be especially challenging to make, as the hallmark of classic IIMs, myositis, is absent. As seen in this case, this patient was repeatedly misdiagnosed with pneumonia despite having progressive symptoms concerning for an underlying multisystem process, highlighting the importance of a well-defined illness script. Since the discovery of the anti-MDA5 antibody in the early 2000s, a specific phenotype associated with this antibody has emerged. Though there are no accepted diagnostic criteria, anti-MDA5 antibody-associated clinically amyopathic dermatomyositis has been defined in studies as having classic cutaneous findings of dermatomyositis without clinical myositis, ILD, and serologic testing positive for the anti-MDA5 antibody. In addition to classic cutaneous findings of dermatomyositis, including heliotrope rash, Gottron's papules, and shawl sign, these patients are prone to ulcerative lesions as noted on this patient's elbows. The ILD in this condition may be rapidly progressive. These patients may also present with prominent inflammatory arthritis. As demonstrated by this case, a thorough review of systems is important when evaluating patients with multisystem disease.

This patient's symptoms, including typical rash, progressive dyspnea, dysphagia, aspiration, Raynaud's, oral ulcers, alopecia, and weight loss, were consistent with dermatomyositis and should prompt pattern recognition and evaluation for an underlying rheumatologic process. As noted above, the lack of clinical myositis often differentiates anti-MDA5 antibody-associated dermatomyositis from other IIMs. Mild presentations of anti-MDA5 antibody-associated dermatomyositis may have cutaneous disease without muscle or lung involvement, while severe presentations include both skin disease and rapidly progressive ILD. In the cases we reviewed, the majority of patients with this disease lacked muscle weakness and tenderness and had normal CK levels (known as clinically amyopathic dermatomyositis).[1, 2] However, other cases describe patients with myopathy to varying degrees. One patient presented with subjective proximal muscle weakness and had a normal CK level, while a second patient endorsed proximal muscle weakness and tenderness with an elevated CK.[3, 4] Thus, anti-MDA5 antibody-associated dermatomyositis usually presents without myositis, but a spectrum of muscle involvement is possible.

With the discovery of an increasing number of myositis-specific antibodies (MSAs), it is now recognized that IIMs represent a spectrum of disease. There are now over fifteen distinct MSAs that are each associated with unique systemic inflammatory manifestations (Table 1).[5] Classifying IIMs by their causative autoantibody helps facilitate diagnostic reasoning in cases that can be diagnostically challenging. A diagnostic schema that organizes IIMs around the presence of myositis makes it difficult for the clinician to recognize cases where evidence of myositis may be lacking, sometimes more broadly defined as clinically amyopathic dermatomyositis (CADM) as noted above. Indeed, the diagnosis of CADM is delayed in over forty percent of patients (as was the case for our patient) since the clinical presentation lacks evidence of myositis, such as proximal muscle weakness, muscle tenderness on exam, and elevation in CK.[6]

Table 1 Selected Myositis-Specific Antibodies*

Myositis-specific antibody	Frequency in myositis	Associated clinical syndrome(s)
Anti-Jo-1	15–30%	Anti-synthetase syndrome (ASS)
Anti-PL-7	5–10%	ASS
Anti-SRP	5–10%	Immune-mediated necrotizing myopathy; polymyositis
Anti-Mi-2	5–10%	Classical dermatomyositis
Anti-TIF1	10–20%	Dermatomyositis (DM), including juvenile and cancer-associated DM
Anti-MDA5	19% of DM	Clinically amyopathic DM; interstitial lung disease

Table 1 presents a selected group of the most common MSAs; this is not a complete list. Adapted from Table 1 in reference 5

Pulmonary involvement (most commonly interstitial lung disease) is common in IIMs (prevalence ranging from 20 to 65% according to one review article) and is a major driver of morbidity and mortality.[7] The pulmonary findings in IIMs can be broadly classified as interstitial lung disease (ILD), but can have a variety of histopathologic appearances including cryptogenic organizing pneumonia (COP), nonspecific interstitial pneumonia (NSIP), usual interstitial pneumonia (UIP), and diffuse alveolar damage (DAD).[7] The autoantibodies that often lead to ILD include the anti-aminoacyl tRNA synthetase antibodies (such as anti-Jo1, anti-PL7, anti-PL12), which cause the antisynthetase syndrome, and the anti-MDA5 antibody, which typically also causes CADM as we have discussed.[8] The severity of pulmonary disease tends to be related to the autoantibody that underlies the process. Of note, the anti-MDA5 antibody is of particular significance as it may be associated with a rapidly progressive phenotype.[7]

In terms of treatment, recent evidence suggests that the treatment paradigm for anti-MDA5 antibody-associated dermatomyositis differs from other inflammatory myopathies, in that it often responds to initial combination therapy with tacrolimus and cyclophosphamide rather than step-wise therapy. For patients who do not respond to the initial combination therapy, expert opinion recommends first adding additional immunosuppressive medications (such as rituximab in the case presented) before utilizing plasmapheresis or IVIG as salvage therapy.[9]

CONCLUSION

This case highlights the importance of recognizing the combination of dermatomyositis rash and rapidly progressive ILD as concerning for clinically amyopathic dermatomyositis. In the case presented, establishing the correct diagnosis was made possible by a thorough history and physical exam. The combination of recurrent admissions for pulmonary complaints associated with a rash and arthritis raised suspicion

for diseases that present with this constellation of findings, namely IIMs and specifically anti-MDA5 antibody-associated amyopathic dermatomyositis. Once a clinical concern for amyopathic dermatomyositis is identified in a patient, an interdisciplinary approach to diagnosis and treatment is crucial. Clinicians should collaborate with laboratory medicine to process a MSA panel to establish the correct diagnosis. Rheumatology and pulmonology specialists should be consulted to help guide management due to the rapid evolution of treatment recommendations. Ultimately, when faced with a patient with skin findings consistent with dermatomyositis and ILD on history or physical exam, the astute diagnostician will consider both classic dermatomyositis and clinically amyopathic dermatomyositis in their pursuit of the correct diagnosis.

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REFERENCES

1. **Parperis K, Kiyani A**. Clinically amyopathic dermatomyositis associated with anti-MDA5 antibody. *BMJ Case Rep*. Jan 4 2018;2018. https://doi.org/10.1136/bcr-2017-222060
2. **Chaisson NF, Paik J, Orbai AM, et al.** A novel dermato-pulmonary syndrome associated with MDA-5 antibodies: report of 2 cases and review of the literature. *Medicine (Baltimore)*. Jul 2012;91(4):220-8. https://doi.org/10.1097/MD.0b013e3182606f0b
3. **Palawisuth S, Kantikosum K, Patiyasikunt M, Sriprasart T, Asawanonda P, Rerknimitr P**. A Bad Sign: Dermatomyositis with Interstitial Lung Disease. *Am J Med*. Feb 2019;132(2):182-186. https://doi.org/10.1016/j.amjmed.2018.09.013
4. **Yashiro M, Asano T, Sato S, et al.** Anti-MDA5 antibody-positive hypomyopathic dermatomyositis complicated with pneumomediastinum. *Fukushima J Med Sci*. 2018;64(2):89-94. https://doi.org/10.5387/fms.2018-01
5. **Vencovský J, Alexanderson H, Lundberg IE**. Idiopathic Inflammatory Myopathies. *Rheum Dis Clin North Am*. Nov 2019;45(4):569-581. https://doi.org/10.1016/j.rdc.2019.07.006
6. **Ghazi E, Sontheimer RD, Werth VP**. The importance of including amyopathic dermatomyositis in the idiopathic inflammatory myositis spectrum. *Clin Exp Rheumatol*. Jan-Feb 2013;31(1):128-34.
7. **Labirua A, Lundberg IE**. Interstitial lung disease and idiopathic inflammatory myopathies: progress and pitfalls. *Curr Opin Rheumatol*. Nov 2010;22(6):633-8. https://doi.org/10.1097/BOR.0b013e32833f1970
8. **Selva-O'Callaghan A, Pinal-Fernandez I, Trallero-Araguás E, Milisenda JC, Grau-Junyent JM, Mammen AL**. Classification and management of adult inflammatory myopathies. *Lancet Neurol*. Sep 2018;17(9):816-828. https://doi.org/10.1016/s1474-4422(18)30254-0
9. **Romero-Bueno F, Diaz Del Campo P, Trallero-Araguás E, et al.** Recommendations for the treatment of anti-melanoma differentiation-associated gene 5-positive dermatomyositis-associated rapidly progressive interstitial lung disease. *Semin Arthritis Rheum*. Jun 1 2020;50(4):776-790. https://doi.org/10.1016/j.semarthrit.2020.03.007