

Antimelanoma differentiation-associated gene 5 dermatomyositis associated with acute encephalopathy



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INTRODUCTION

Antimelanoma differentiation-associated gene 5 (MDA5) dermatomyositis is a recently described disease entity that presents with distinct mucocutaneous and systemic features.¹ In this case report, we describe a patient with anti-MDA5 dermatomyositis who presented with interstitial lung disease (ILD), classic cutaneous findings, and acute encephalopathy.

CASE REPORT

A 57-year-old man with diabetes mellitus type II, a recent 30-pound weight loss, and a 6-month history of ILD was admitted with acutely altered mental status. In the 3 to 4 weeks immediately before admission, he was noted to have recurrent fevers, myalgias, weakness, increasing oxygen requirement, progression of lung disease on imaging, and rapidly declining mental status after completing a several-months-long prednisone taper from 40 to 5 mg. The patient denied any other medication changes or recent illnesses. Upon admission, the patient exhibited tangential speech and nonsensical replies, and was oriented only to self. His cranial nerve examination, reflexes, sensation, and coordination were within normal limits. Muscle tone was mildly increased in the upper extremities with decreased muscle bulk. During admission, he was acutely hypoxic with exertion to an oxygen saturation in the low 80s and required 2 L of oxygen via nasal cannula.

Abbreviations used:

CNS:	central nervous system
ILD:	interstitial lung disease
MDA5:	melanoma differentiation-associated gene 5

Dermatology was consulted for evaluation of painful erythematous palmar papules with digital ulcerations. The patient's wife first noted these skin changes around the time of his ILD diagnosis. Physical examination was notable for a mild helio-trope rash, Gottron's sign on the elbows and knees, and ulcerated palmar and digital macules and papules (Fig 1, A). Biopsy of the left second digit demonstrated focal vasculopathy with a thickened basement membrane zone and increased mucin, suggestive of a connective tissue disease process (Fig 2). A myomarker 3 panel was sent and confirmed the presence of anti-MDA5 antibodies (117 units, reference <20). The autoimmune workup was notable for positive antinuclear antibody (1:640) with negative reflex panel, mildly elevated aldolase, and negative antiphospholipid antibodies and rheumatoid factor. Ferritin was markedly elevated to 4089 ng/mL, while other inflammatory markers (C-reactive protein, erythrocyte sedimentation rate, C4 complement, and haptoglobin) were moderately elevated and creatinine kinase and C3 complement were within normal limits. An extensive infectious

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Fig 1. Cutaneous ulcerations involving the palms of both hands. **A**, Hands before treatment. **B**, Hands after 5 weeks of prednisone treatment.

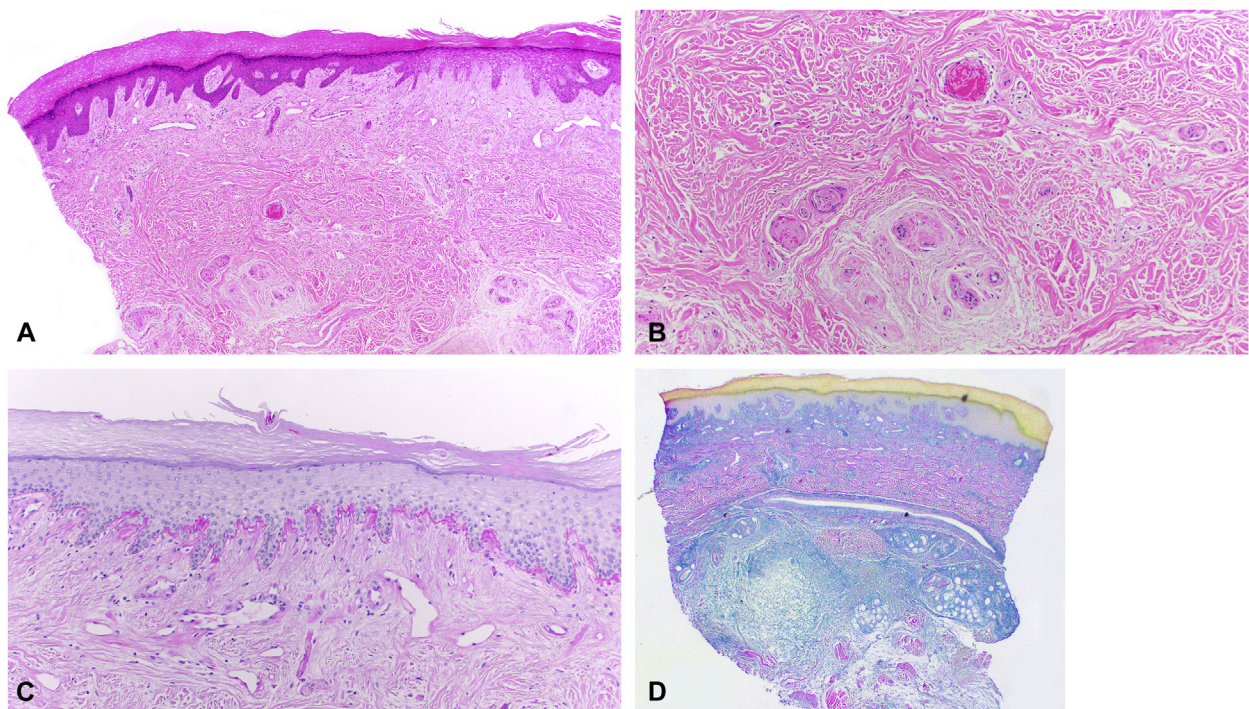


Fig 2. Biopsy of the left second digit. **A**, Biopsy of palmar surface of the digit demonstrating a pauci-inflammatory process with telangiectasia. **B**, Focal intraluminal fibrin thrombi are present within the mid reticular dermis. **C**, A thickened basement membrane zone is noted. **D**, Increased mucin deposition is present in the superficial dermis and extends into the subcutis. (**A** and **B**, Hematoxylin-eosin stain; **C**, periodic-acid-Schiff-diastase stain; and **D**, colloidal iron stain; original magnifications: **A**, $\times 40$; **B**, $\times 100$; **C**, $\times 100$; **D**, $\times 25$.)

and neurologic workup for the patient's acute encephalopathy was unrevealing. The infectious workup was unremarkable, including negative blood culture, HIV, syphilis, aspergillus, beta-d glucan, hepatitis serologies, and quant gold tests. The neurologic workup revealed no evidence of central nervous system (CNS) vasculitis on magnetic resonance imaging and magnetic resonance

angiography of the brain. An electroencephalogram demonstrated findings consistent with moderate encephalopathy and no seizure-like activity. A lumbar puncture was performed, and cerebral spinal fluid studies (protein, glucose, cell counts) were within normal limits. Meningitis, paraneoplastic, Creutzfeldt-Jakob, and autoimmune encephalopathy panels were negative. Heavy metal panel was

negative; vitamin and mineral studies (zinc, copper, ceruloplasmin folate, vitamin B₁₂, and vitamin D) as well as iron studies were within the normal range.

The patient was initially started on prednisone 50 mg daily and subsequently tacrolimus 1 mg twice daily, hydroxychloroquine 300 mg daily, and aspirin 81 mg daily. Five weeks after starting prednisone, the patient noted improvement in his cutaneous ulcerations (Fig 1, B), and his family noted that his mentation had dramatically improved. He had slight improvement in his rapidly progressive ILD, with improved oxygen saturation to an average of 96% and modest improvement on imaging and pulmonary function tests after starting the aforementioned therapies. He has not needed supplemental oxygen.

DISCUSSION

Anti-MDA5 dermatomyositis is a hypopathic or amyopathic subtype of dermatomyositis with a unique phenotype that includes cutaneous and oral ulcerations, painful palmar papules, alopecia, panniculitis, and an elevated risk of rapidly progressive ILD.¹ The associated ILD has a potentially fatal course. Dermatologists can have an important role in diagnosis and expedited management by recognizing cutaneous findings, since the presence of cutaneous ulcers is the strongest predictor of ILD.² Ulcers develop in up to 82% of cases, with a predilection for the digital pulp, as was seen in this patient. Painful palmar papules are a second distinct feature, frequently appearing as inflammatory patches on a purple or livedoid background over the metacarpophalangeal or interphalangeal joint creases.

The pathogenesis of this variant is thought to be due to an occlusive vasculopathy of the skin and pulmonary vasculature. Clinicopathologic correlation is important, since the vasculopathy noted in biopsies may also be seen in other hypercoagulable states, such as antiphospholipid antibody syndrome. Treatments such as aspirin, hydroxychloroquine, and calcium channel blockers may be beneficial to help prevent vasculopathy-induced ulcerations. Additional therapies include high-dose oral steroids, intravenous immunoglobulin, tacrolimus, and rituximab.

The initial differential diagnosis for the patient's acutely altered mental status was quite broad and included possible paraneoplastic processes and autoimmune or infectious encephalopathy. Given his extensive negative workup, however, and his dramatic cognitive improvement with

immunosuppressive therapy, an inflammatory etiology associated with anti-MDA5 dermatomyositis is the presumed diagnosis. Although there is a strong association between dermatomyositis and malignancy, the anti-MDA5 subtype reportedly has a reduced risk of malignancy.²

Neurologic manifestations in dermatomyositis, including neuromyelitis optica, CNS vasculopathy, and encephalomyelitis, have rarely been reported in the literature.³⁻⁵ Similar to Susac syndrome, an autoimmune endotheliopathy, characterized by the triad of encephalopathy, hearing loss, and branch retinal artery occlusion, the CNS manifestations of dermatomyositis may be the result of microvascular injury.⁶ Anti-MDA5 dermatomyositis also has parallels to lupus cerebritis, a condition that manifests with neuropsychiatric symptoms (acute confusional state, cognitive dysfunction, and mood changes) associated with systemic lupus erythematosus. Lupus cerebritis has a proposed pathogenesis of CNS inflammatory response similar to the encephalopathy reported here.

We present this case of anti-MDA5 dermatomyositis associated with ILD and a novel systemic manifestation of dermatomyositis in the form of acute encephalopathy, a presentation with which dermatologists should be familiar for timely diagnosis and treatment.

Conflicts of interest

None disclosed.

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