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Anti-MDA-5 negative, anti-Ku positive clinically amyopathic dermatomyositis

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Abstract

We present a patient with anti-MDA5 negative, anti-Ku positive clinically amyopathic dermatomyositis (CADM). A 61-year-old woman presented with a chief complaint of a 20-year history of a pruritic rash that was active on her face, chest, hands, legs, and back. A mildly scaly, erythematous, photo-distributed eruption along with slightly violaceous, scaly papules accentuated on the wrist, metacarpophalangeal joints, proximal interphalangeal and distal interphalangeal joints. Antibody profile was significant for positive ANA and anti-dsDNA, elevated anti-TIF-1gamma (RDL)/p155, and weakly positive anti Ku. Biopsy was consistent with dermatomyositis. Melanoma differentiation-associated gene 5 antibody (anti-MDA-5) has been identified as the most commonly associated autoantibody found in CADM and is associated with poor prognosis and a biomarker for the diagnosis of rapidly progressive interstitial lung disease. To our knowledge, our patient is the first case of negative anti-MDA-5 and anti-Ku positive CADM.

Keywords: antibodies, autoimmune disorder, dermatomyositis

Introduction

Clinically amyopathic dermatomyositis (CADM) is an inflammatory autoimmune disease with cutaneous manifestations of dermatomyositis but no or minimal muscle involvement [1]. We present a patient with negative melanoma differentiation-associated gene 5 antibody (anti-MDA5) and anti-Ku positive CADM.

Case Synopsis

A 61-year-old woman with a past medical history of type two diabetes mellitus, longstanding history of atopic dermatitis (not biopsy confirmed), major depressive disorder, and hyperlipidemia presented with a chief complaint of a rash that was currently active on her face, chest, hands, legs, and back. She noted that the rash had been present for over 20 years and was pruritic. Prior treatment had included topical corticosteroids, most recently fluocinolone to the scalp and hydrocortisone to the trunk and extremities. In addition, intramuscular triamcinolone injections had been administered without improvement. Interestingly, prior to presentation, she had recently received 20 treatments of excimer laser (narrow-band UVB) with some improvement, but did note persistent flaring. Medication allergies included fluconazole and there was no personal or family history of skin cancer. Review of systems was positive for arthralgia and back pain and negative for fever, fatigue, unintentional weight loss, weakness, or myalgias. The patient's systemic medications included fenofibrate, metformin, sertraline, simvastatin, and alendronate.

On examination, the patient was found to have erythematous, photo-distributed, slightly infiltrated plaques and scattered papules along the forehead,

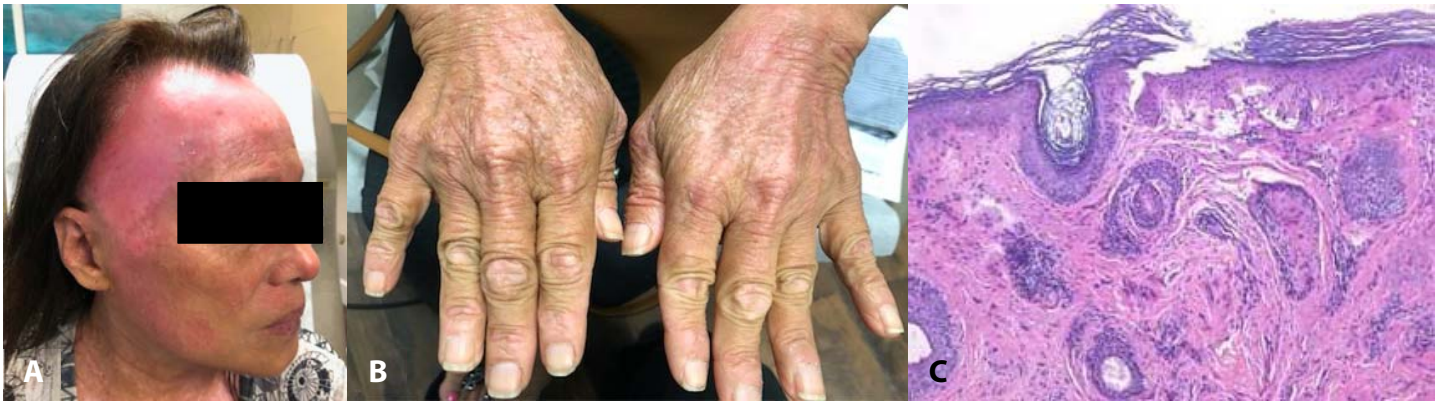

Figure 1. ***A)*** *Erythematous, scaly, slightly infiltrated plaques and scattered papules in a photodistributed pattern along the forehead, temples, and cheeks. Recent excimer laser treatment likely contributed to the marked erythema of the forehead.* ***B)*** *Slightly violaceous, scaly papules accentuated on the wrist, metacarpophalangeal joints, proximal interphalangeal joints, and distal interphalangeal joints associated with ragged cuticles and sparse dilated capillaries on the bilateral dorsal hands.* ***C)*** *Biopsy of the right upper cutaneous lip showed interface dermatitis with superficial and deep perivascular and periadnexal inflammation and thickened basement membranes.*

temples, posterior neck, upper back, chest, and cheeks with minimal scale (**Figure 1A)** and notable sparing of the photoprotective areas. She also presented with slightly violaceous, scaly papules accentuated on the wrist, metacarpophalangeal joints, proximal interphalangeal joints, and distal interphalangeal joints associated with ragged cuticles and sparse dilated capillaries on the bilateral dorsal hands (**Figure 1B)**. Strength assessment revealed 5/5 strength throughout.

Creatinine kinase, aldolase, AST, and ALT were all within normal limits. Accordingly, muscle MRI, biopsy, or EMG were not done. Antibody profile was significant for a positive ANA titer, 1:1280, speckled (negative <1:40), positive anti-dsDNA 10 IU/mL (normal≤4 IU/mL), elevated anti-TIF-1gamma (RDL)/p155 (25Units, (normal <20Units), and weakly positive anti Ku (normal-negative). Biopsy was performed on the right upper cutaneous lip to avoid areas previously treated with excimer laser. Histological inspection revealed interface dermatitis with superficial and deep perivascular and periadnexal inflammation with thickened basement membrane, consistent with dermatomyositis (**Figure 1C)**. Malignancy work-up was negative for ovarian, pulmonary, or pelvic pathology malignancy. CT pelvis showed concern for bilateral femoral head avascular necrosis, but was otherwise negative. Pulmonary function test was ordered to assess for pulmonary involvement, but was not completed owing to the COVID-19 pandemic. The patient declined shortness of breath, cough, or other respiratory symptoms. She was started on hydroxychloroquine 200mg twice daily as well as triamcinolone 0.1 % cream topically. However, the patient discontinued the hydroxychloroquine secondary to worsening of itch. She was then started

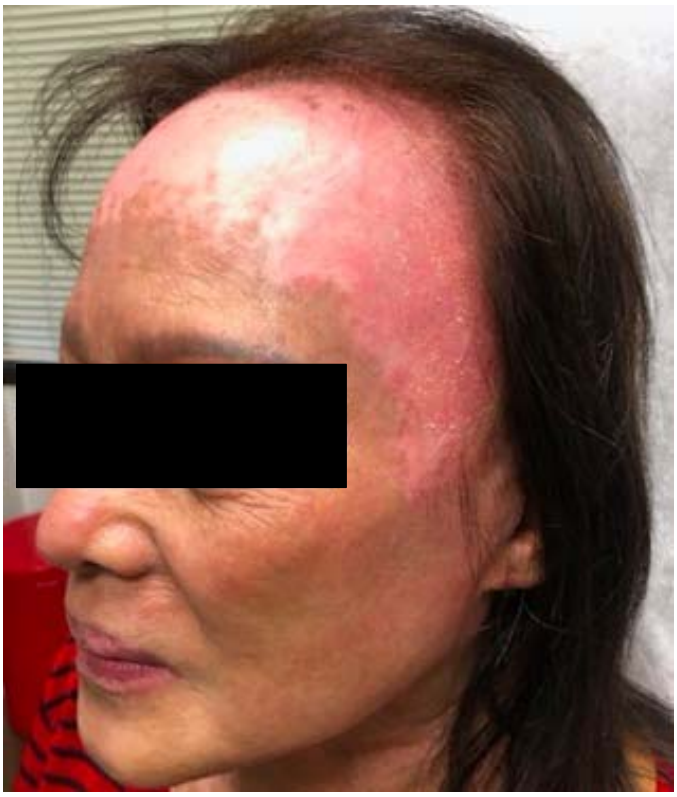

Figure 2. *Patient at 6-week follow up, showing improvement while on methotrexate 15mg weekly.*

on methotrexate 15mg weekly with improvement (**Figure 2**). Systemic corticosteroids were avoided given the possible avascular necrosis of femoral head seen on the pelvic CT.

Case Discussion

Clinically amyopathic dermatomyositis is further classified as hypomyopathic or amyopathic dermatomyositis. The former lacks clinical evidence of muscle weakness, yet laboratory investigation, EMG, or muscle biopsy confirms muscle involvement. The latter also has no clinical evidence of muscle weakness but also lacks laboratory, biopsy, or EMG evidence of underlying muscle inflammation [2]. The pathognomonic skin manifestations of CADM are similar to that of dermatomyositis, including Gottron papules (**Figure 1B, C)**, heliotrope rash, and shawl sign on the posterior neck, shoulders, and upper back. A photodistributed exanthem, alopecia, and periungual telangiectasias are well-described [2,3].

Melanoma differentiation-associated gene 5 antibody (anti-MDA-5) has been identified as the most commonly associated autoantibody found in CADM [4,5] and is associated with poor prognosis. It is a biomarker for the diagnosis of rapidly progressive interstitial lung disease (ILD), [1,2]. In fact, anti-MDA5+ dermatomyositis (DM) patients who developed rapidly progressive ILD had higher anti-MDA5 antibody levels compared to those without rapidly progressive ILD [5]. To our knowledge, our patient is the first reported with negative anti-MDA-5 and anti-Ku positive CADM.

Melanoma differentiation-associated gene 5 is a RIG-1-like receptor dsRNA helicase enzyme encoded in the *IFIH1* gene and functions as a virus sensor by pattern recognition receptor for dsRNA [6]. In both Japanese and North American DM patients, anti-MDA-5 positive DM patients have also been shown to have an increased frequency of rare, acral ulcerative skin changes [6]. Arthralgias are common in patients with positive anti-MDA-5 [5]. A cohort study reported hand swelling in 40% and arthritis/arthralgia in 70% of 77 patients with DM patients [7], whereas Hall noted that 9 of 11 anti-MDA-5+ DM patients had a symmetric inflammatory polyarthropathy resembling rheumatoid arthritis [8]. Interestingly, whereas our anti-MDA-5-negative patient did experience arthralgias, her rheumatoid factor, erythrocyte sedimentation rate, and C-reactive protein were negative.

Ku protein is a DNA-binding protein involved in DNA repair. Anti-Ku antibodies have been reported in several auto-immunity conditions, including myositis, systemic lupus erythematosus (SLE), and Sjögren syndrome [9]. Inflammatory myopathies with anti-Ku antibodies are commonly seen in an overlap syndrome with different connective autoimmune diseases, such as scleroderma and SLE; in addition, reports of anti-Ku positive inflammatory myopathies have found significant associations with ILD [10]. Interestingly, our patient presented with a weak anti-Ku antibody and absence of myopathy or scleroderma symptoms, which, to our knowledge, has not been reported in the literature.

Currently, classification criteria do not require the presence of myositis-specific antibodies or myositis-associated antibodies to diagnose CADM [3]. In addition, cutaneous lupus and CADM antibody profile can overlap, as in our patient with a positive anti-dsDNA.

A variety of malignancies have been found to be associated with CADM. A comprehensive review found CADM to have similar associated malignancies to classic dermatomyositis, such as genitourinary and respiratory malignancies [11]. However, this review also showed that breast cancer was the most commonly reported neoplasm in CADM, whereas lung cancer was the most commonly observed malignancy in classic dermatomyositis [11].

Patients with dermatomyositis are at the highest risk of having an underlying malignancy during the first five years of diagnosis. Despite conflicting studies on malignancy risk in DM versus CADM, age appropriate cancer screening is still recommended in CADM patients [3]. Regarding cancer screening, there is no consensus regarding the recommended frequency or extent of evaluation for patients with CADM or DM. However, given the higher association of

pulmonary pathologies, including rapidly progressive ILD, in CADM patients frequent evaluations could prove beneficial.

Conclusion

This is a unique case of CADM with an absence of anti-MDA-5 and presence of anti-Ku antibodies. This presentation reflects of the necessity of evaluating for complications and brings up the discussion of ideal cancer screening guidelines.

Potential conflicts of interest

RKS serves as a scientific advisor for LearnHealth and Arbonne and as a consultant to Burt's Bees, Physicians Exclusive, Nutrafol, Abbvie, Leo, Sun and Regeneron Pharmaceuticals.

References

1. Takada T, Asakawa K, Barrios R. A Japanese-American female with rapidly progressive interstitial lung disease associated with clinically amyopathic dermatomyositis. *Clin Rheumatol*. 2020;40:1159-1165. [PMID: 32676922].
2. Tartar DM, Chung L, Fiorentino DF. Clinical significance of autoantibodies in dermatomyositis and systemic sclerosis. *Clin Dermatol*. 2018;36:508–24. [PMID: 30047434].
3. Concha JSS, Tarazi M, Kushner CJ, Gaffney RG, Werth VP. The diagnosis and classification of amyopathic dermatomyositis: a historical review and assessment of existing criteria. *Br J Dermatol*. 2019;180:1001–8. [PMID: 30561064].
4. Sato S, Hirakata M, Kuwana M, et al. Autoantibodies to a 140-kd polypeptide, CADM-140, in Japanese patients with clinically amyopathic dermatomyositis. *Arthritis Rheum*. 2005;52:1571–6. [PMID: 15880816].
5. Moghadam-Kia S, Oddis CV, Aggarwal R. Anti-MDA5 Antibody Spectrum in Western World. *Curr Rheumatol Rep*. 2018;20:78. [PMID: 30382445].
6. Sontheimer RD. MDA5 autoantibody-another indicator of clinical diversity in dermatomyositis. *Ann Transl Med*. 2017;5:160. [PMID: 28480196].
7. Fiorentino D, Chung L, Zwerner J, Rosen A, Casciola-Rosen L. The mucocutaneous and systemic phenotype of dermatomyositis patients with antibodies to MDA5 (CADM-140): a retrospective study. *J Am Acad Dermatol*. 2011;65:25–34. [PMID: 21531040].
8. Hall JC, Casciola-Rosen L, Samedy L-A, et al. Anti-melanoma differentiation-associated protein 5-associated dermatomyositis: expanding the clinical spectrum. *Arthritis Care Res* . 2013;65:1307–15. [PMID: 23436757].
9. Belizna C, Henrion D, Beucher A, et al. Anti-Ku antibodies: Clinical, genetic and diagnostic insights. *Autoimmun Rev*. 2010;9:691–4. [PMID: 20621654].
10. Rigolet A, Musset L, Dubourg O, et al. Inflammatory myopathies with anti-Ku antibodies: a prognosis dependent on associated lung disease. *Medicine* . 2012;91:95–102. [PMID: 22391471].
11. Udkoff J, Cohen PR. Amyopathic Dermatomyositis: A Concise Review of Clinical Manifestations and Associated Malignancies. *Am J Clin Dermatol*. 2016;17:509–18. [PMID: 27256496].