Expanding the clinical phenotype of nuclear matrix protein 2 antibody-positive dermatomyositis

Michelle Toker, BS,[a] Roya S. Nazarian, MD,[a] Pooja Srivastava, MD,[b] Bijal Amin, MD,[a,b] and Benedict Wu, DO, PhD[a]

Key words: autoimmune connective tissue disease; dermatomyositis; inflammatory disease; morphology; nuclear matrix protein 2 (NXP-2); rash.

INTRODUCTION

Nuclear matrix protein 2 (NXP-2) antibody-positive dermatomyositis (DM) is a subset of DM with a distinct clinical presentation and prognosis. Anti-NXP-2 antibody positivity is prevalent in approximately 1% ~ 17% of adult DM patients and is more common among male and younger DM patients.[1-4] As circulating autoantibodies in DM have the propensity to be mutually exclusive, other common myositis-specific antibodies, such as anti-Mi-2, anti-MDA-5, and anti-Jo-1, may be negative in patients with the NXP-2 subset.[5,6] The classic systemic phenotype of NXP-2 DM is characterized by severe muscle weakness, high creatine kinase, calcinosis, dysphagia, subcutaneous edema, and minimal interstitial lung disease.[1-4,6-8] Polymorphous cutaneous findings, however, have also been reported. We aim to expand upon previously reported cutaneous findings by presenting an atypical case of NXP-2 DM.

Abbreviations used:

ACR:	American College of Rheumatology
DM:	dermatomyositis
EULAR:	European Alliance of Associations for Rheumatology
NXP-2:	nuclear matrix protein 2

CASE PRESENTATION

A 77-year-old Caucasian woman presented with a 5-month history of multiple erythematous pink to red, ovoid, smooth, thin papules and plaques affecting her chest and upper extremities (Fig 1). The lesions were intermittently pruritic and nontender. Finger and periungual examinations revealed proximal nailfold erythema, periungual telangiectasias, and dilated capillary loops with dropout (Fig 2). A comprehensive skin exam was negative for heliotrope rash, shawl or V-neck erythema, Gottron papule/sign, and calcinosis. She endorsed muscle weakness, arthralgias, dysphagia, and Raynaud's phenomenon of her fingers, sparing the thumbs. In addition, she reported bilateral lower leg and thigh swelling, which coincided with the rash onset, but has since resolved. Notably, she denied shortness of breath. Skin biopsy of the plaque revealed interface vacuolar dermatitis with increased dermal mucin (Fig 3). Laboratory studies were notable for anti-NXP-2 antibody positivity, antinuclear antibody positivity with a reported titer of >1:1280, and mildly elevated erythrocyte sedimentation rate (40 mm/h). Complement, C-reactive protein, aldolase, and creatine kinase levels were within normal limits. Other myositis-specific antibodies, including anti-Jo-1, anti-PM, anti-PL, anti-Mi-2, and anti-MDA-5, were

From the Division of Dermatology, Montefiore Medical Center, Albert Einstein College of Medicine, Bronx, New York[a]; and Department of Pathology, Montefiore Medical Center, Albert Einstein College of Medicine, Bronx, New York.[b]

Funding sources: None.

IRB approval status: Not applicable.

Patient consent: Consent for the publication of all patient photographs and medical information was provided by the authors at the time of article submission to the journal stating that all patients gave consent for their photographs and medical information to be published in print and online and with the understanding that this information may be publicly available.

Correspondence to: Michelle Toker, BS, Montefiore Medical Center, Albert Einstein College of Medicine, 1300 Morris Park Avenue, Bronx, NY 10461. E-mail: michelle.toker@einsteinmed.edu.

JAAD Case Reports 2023;33:77-80.

2352-5126

https://doi.org/10.1016/j.jdcr.2023.01.019

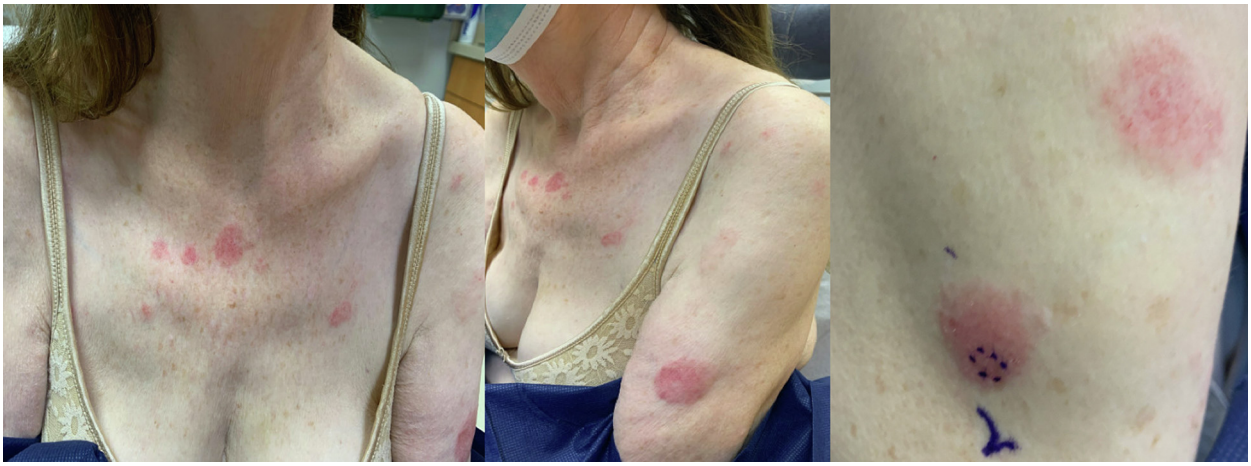

Fig 1. Multiple discrete, round, smooth, erythematous pink to red papules and plaques affecting the chest and bilateral upper extremities.

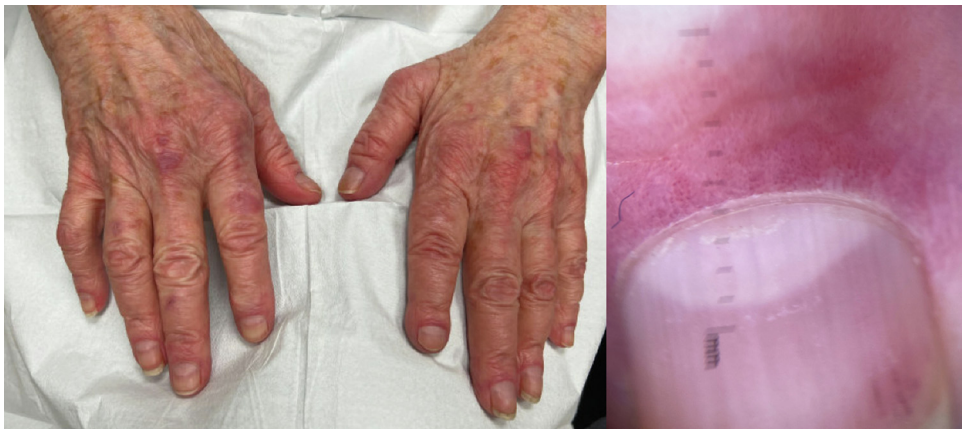

Fig 2. Proximal nailfold erythema and periungual telangiectasias with dilated capillary loops and dropout.

negative. A thorough musculoskeletal examination by the rheumatology service revealed no objective muscle weakness or joint disease; the patient had normal muscle strength and full range of motion. With these findings, she was ultimately diagnosed with amyopathic NXP-2 DM.

Evaluation for interstitial lung disease and malignancy with computed tomography of the head, chest, abdomen, and pelvis and complete blood count was negative. Further workup for gastrointestinal and gynecologic malignancies is pending. At 1 month follow-up, the patient's rash nearly resolved with topical triamcinolone and tacrolimus.

DISCUSSION

The cutaneous manifestations of NXP-2 DM are heterogenous in the literature and stray from the common skin findings of DM (Table I).

Some studies have reported milder skin involvement in anti-NXP-2 DM patients, with reduced frequencies of Gottron papules, shawl or V-neck signs, nailfold changes, and erythema with or without scaling of the elbows and knees.[1,3] Furthermore, the NXP-2 antibody phenotype has been associated with the absence of skin findings or nonspecific skin rashes atypical for DM.[8,9] Interestingly, one study found that anti-NXP-2 DM patients were more likely to exhibit heliotrope rash compared to other DM patients.[4]

In addition to unique cutaneous manifestations, NXP-2 DM is known for its association with increased risk of malignancy. NXP-2 is involved in the activation and localization of the p53 tumor suppressor gene and has subsequently been implicated in DM-associated malignancy, including prostate, lung, and pancreatic cancer, among others.[1] Patients with NXP-2 antibodies are believed to carry a greater than

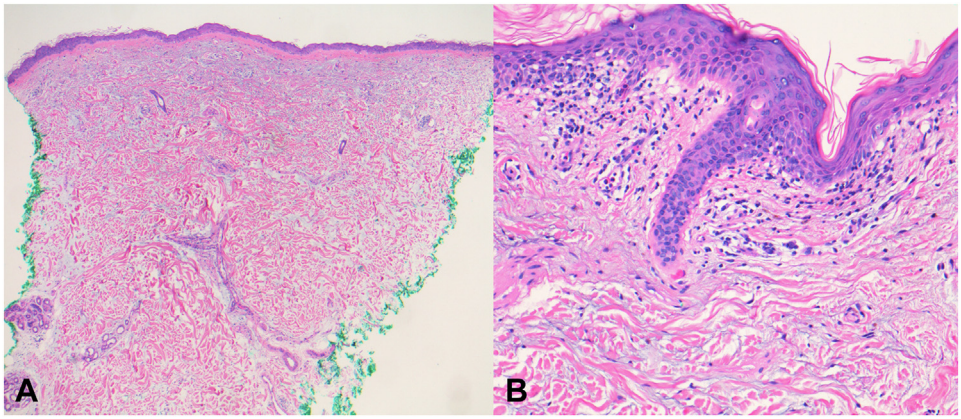

Fig 3. A, Hematoxylin and Eosin-stained section (20×) showing subtle vacuolar interface dermatitis and increased dermal mucin. **B,** Hematoxylin and Eosin-stained section (200×) showing vacuolar interface dermatitis and increased dermal mucin. The inflammatory cell infiltrate consists of lymphocytes and histiocytes as well as melanophages. (**A** and **B,** Hematoxylin-eosin stain; original magnifications: **A**, ×20; **B**, ×200.)

Table I. Common dermatomyositis skin findings with associated morphologies

Physical exam finding	Morphology and distribution
Head and neck	
Heliotrope rash*	Macular, confluent, violaceous patches over the eyelids, with or without edema
V-neck erythema	Erythematous, poikilodermatous macules and patches on the V-area of the neck
Shawl sign	Erythematous, poikilodermatous macules and patches on the nape of the neck and shoulders
Upper and lower extremities	
Gottron papules/sign*	Erythematous macules and patches (sign) or violaceous papules on dorsal aspect of joints
Holster sign	Erythematous, poikilodermatous macules and patches on the lateral hips and upper thighs

*Signifies the pathognomonic dermatomyositis skin findings.

3-fold increased risk of cancer compared to the general population.[7] Therefore, although our patient had a normal initial cancer workup, she continues to be monitored for the development of malignancy.

The current case represents a previously unreported cutaneous manifestation of photodistributed discrete, thin, round papules and plaques. Additionally, despite the classic association of NXP-2 DM with impressive muscle involvement, our patient lacked objective evidence of muscle weakness and elevated muscle enzymes. According to the EULAR/ACR criteria, the diagnosis of amyopathic DM may be established if the following criteria are met: interface pathology on skin biopsy, positive myositis-specific antibodies, and no objective muscle involvement.[10] Therefore, our patient was diagnosed with amyopathic NXP-2 DM. To our knowledge, NXP-2 DM presenting as discrete photodistributed, thin, erythematous papules and plaques with no objective musculoskeletal findings has not been previously reported. Therefore, this case contributes to the growing body of literature describing the heterogenous manifestations of this rare DM subtype.

Conflicts of interest

None disclosed.

REFERENCES

1. Ichimura Y, Matsushita T, Hamaguchi Y, et al. Anti-NXP2 autoantibodies in adult patients with idiopathic inflammatory myopathies: possible association with malignancy. *Ann Rheum Dis*. 2012;71(5):710-713.
2. Yan TT, Zhang X, Yang HH, et al. Association of anti-NXP2 antibody with clinical characteristics and outcomes in adult dermatomyositis: results from clinical applications based on a myositis-specific antibody. *Clin Rheumatol*. 2021;40(9):3695-3702.
3. Rogers A, Chung L, Li S, Casciola-Rosen L, Fiorentino DF. Cutaneous and systemic findings associated with nuclear matrix protein 2 antibodies in adult dermatomyositis patients. *Arthritis Care Res (Hoboken)*. 2017;69(12):1909-1914.
4. Ceribelli A, Fredi M, Taraborelli M, et al. Anti-MJ/NXP-2 autoantibody specificity in a cohort of adult Italian patients

with polymyositis/dermatomyositis. *Arthritis Res Ther*. 2012; 14(2):R97.

5. Fiorentino DF, Chung LS, Christopher-Stine L, et al. Most patients with cancer-associated dermatomyositis have antibodies to nuclear matrix protein NXP-2 or transcription intermediary factor 1γ. *Arthritis Rheum*. 2013;65(11):2954-2962.
6. Biddle K, Taylor MD, Linstead SE, Kiely PDW. The utility of myositis specific antibodies in clinical practice. *J Appl Lab Med*. 2022;7(5):1189-1201.
7. Albayda J, Pinal-Fernandez I, Huang W, et al. Antinuclear matrix protein 2 autoantibodies and edema, muscle disease, and malignancy risk in dermatomyositis patients. *Arthritis Care Res (Hoboken)*. 2017;69(11):1771-1776.
8. Li S, Sun C, Zhang L, et al. Clinical heterogeneity of patients with antinuclear matrix protein 2 antibody-positive myositis: a retrospective cohort study in China. *J Rheumatol*. 2022;49(8): 922-928.
9. Inoue M, Tanboon J, Hirakawa S, et al. Association of dermatomyositis sine dermatitis with anti-nuclear matrix protein 2 autoantibodies. *JAMA Neurol*. 2020;77(7):872-877.
10. Waldman R, DeWane ME, Lu J. Dermatomyositis: diagnosis and treatment. *J Am Acad Dermatol*. 2020;82(2):283-296.