



Refractory Digital Ulcers Treated by Botulinum Toxin and Endothelin Receptor-1 Antagonist in Anti-MDA5-Antibody-Positive Dermatomyositis

Hong Ki Min^a
Hae-Rim Kim^b
Sang-Heon Lee^b
Sung-Hye Park^c
Jeeyoung Oh^d
Kyomin Choi^d

^aDivision of Rheumatology,
Department of Internal Medicine,
Konkuk University Medical Center,
Seoul, Korea

^bDivision of Rheumatology,
Department of Internal Medicine,
Konkuk University Medical Center,
Konkuk University School of Medicine,
Seoul, Korea

^cDepartment of Pathology,
Seoul National University Hospital,
Seoul University College of Medicine,
Seoul, Korea

^dDepartment of Neurology,
Konkuk University Medical Center,
Konkuk University School of Medicine,
Seoul, Korea

Dear Editor,

Dermatomyositis (DM) is a type of myositis that presents with proximal muscle weakness and typical dermatologic manifestations.¹ Among myositis-specific autoantibodies, anti-melanoma-differentiation-associated gene 5 (anti-MDA5) antibody (Ab) is specifically identified in clinically amyopathic DM, and is associated with rapidly progressive interstitial lung disease.¹ Anti-MDA5-Ab-positive DM patients exhibit atypical skin lesions such as digital ulcers, acral digital necrosis, or palmar papules, rather than classical dermatologic manifestations.^{1,2} Immunosuppressants and glucocorticoids are used to treat inflammatory myositis, but how to treat digital ulcers has not been established in anti-MDA5-Ab-positive DM. Here we present a patient with anti-MDA5-Ab-positive DM with refractory digital ulcers who responded excellently to treatment with a combination of endothelin receptor-1 antagonist (ERA) and botulinum toxin injection.

A 48-year-old male presented with a 6-month history of muscle weakness and facial discoloration. The facial discoloration was unlikely to be heliotrope rash since it appeared as a brownish color over the entire face. A neurologic examination revealed proximal muscle weakness, with MRC grade 4 in bilateral shoulder abduction and hip flexion. An electrodiagnostic study revealed early recruited myopathic motor-unit action potentials and positive sharp waves. The serum level of creatinine kinase was normal, at 185 units/L reference range 58–348 units/L. A muscle biopsy showed mild myopathic change without inflammatory cell infiltration (Fig. 1A). However, electron microscopy revealed tubuloreticular cytoplasmic inclusions of endothelial cells, which are mostly found in DM among inflammatory myositis³ (Fig. 1B). The classical dermatologic manifestation of DM was absent, but both hands showed cyanotic change and multiple digital ulcers (Fig. 1C). Chest CT revealed multiple subpleural ground glass opacities and consolidations in both lower lung fields. Perfusion scintigraphy of the hand showed a clear decrease in blood flow after cold stimulation. We investigated myositis specific autoantibodies for Mi-2, TIF1γ, MDA5, NXP2, SAE1, Ku, PM-Scl100, PM-Scl75, SRP, PL-7, PL-12, EJ, OJ, and Ro-52 using an immunoblot assay kit (Immunoblot-PreQ system, EUROIMMUN Co., Ltd., Luebeck, Germany), which showed strong positivity only against MDA5.

The patient was started on glucocorticoid therapy comprising 1 g of methylprednisolone for 5 days followed by 1 mg/kg oral prednisolone for 1 month. This treatment was effective against the muscle weakness, but it aggravated the digital ulcers and Raynaud's phenomenon. The intravenous administration of prostacyclin, nifedipine, and phosphodiesterase type 5 inhibitor had no effect. Considering the treatment choice for refractory digital ulcers in systemic sclerosis, oral ERA, bosentan (62.5 mg twice daily), and the injection of botulinum toxin [10 IU of Meditoxin (Medytox, Seoul, Korea) dissolved in 0.1 mL of saline] into

Received July 19, 2019
Revised August 14, 2019
Accepted August 14, 2019

Correspondence

Kyomin Choi, MD
Department of Neurology,
Konkuk University Medical Center,
Konkuk University School of Medicine,
120-1 Neungdong-ro, Gwangjin-gu,
Seoul 05030, Korea
Tel +82-2-2030-7544
Fax +82-2-2030-5169
E-mail kyominchoi@naver.com

© This is an Open Access article distributed under the terms of the Creative Commons Attribution Non-Commercial License (<https://creativecommons.org/licenses/by-nc/4.0>) which permits unrestricted non-commercial use, distribution, and reproduction in any medium, provided the original work is properly cited.

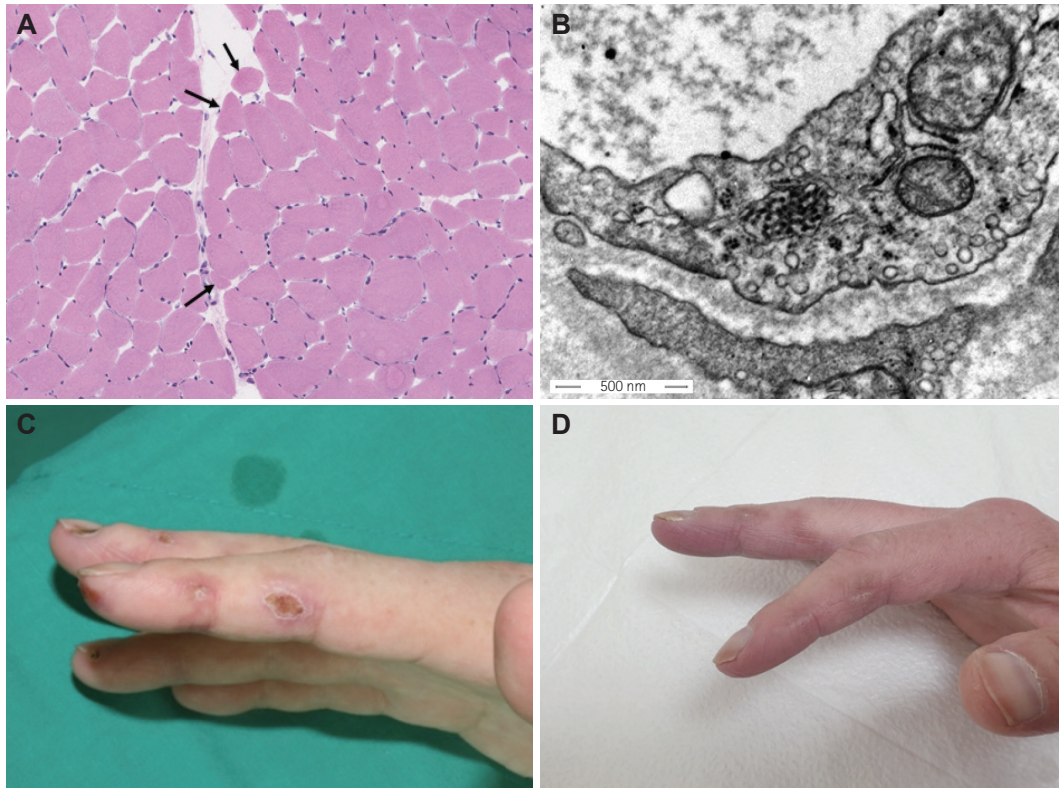


Fig. 1. Muscle biopsy and dermatologic manifestations of the anti-MDA5-Ab-positive dermatomyositis patient. A: Hematoxylin and eosin staining of the vastus lateralis muscle showed minimal size variations of myofibers and revealed some atrophic myofibers (arrows) in the perifascicular area. There was no inflammatory cell infiltration in the endomysium or blood vessels (scale bar: 200 μ m). B: Ultrastructurally, tubuloreticular cytoplasmic inclusions were found in endothelial cells (uranyl acetate and lead citrate stain, scale bar: 500 nm). C: Baseline multiple digital ulcers on the right second finger. D: Applying oral bosentan and botulinum toxin injection resulted in the digital ulcers improving at 12 weeks after the first injection of botulinum toxin.

the soft tissue of the palm proximal to the A1 pulley were attempted. Bosentan and botulinum toxin injections weekly for 3 weeks significantly improved the digital ulcers and Raynaud's phenomenon. The improvement was maintained for 12 weeks after the initial injection of botulinum toxin (Fig. 1D).

Muscle weakness is usually mild or absent and there is lower elevation of muscle enzymes in anti-MDA5-Ab-positive DM patients.⁴ The first-line therapy for digital ulcers and Raynaud's phenomenon are conservative care and vasodilators, with ERA and botulinum toxin injection considered in refractory cases.⁵ Endothelin is a potent vasoconstrictor, and ERA shows a preventive effect against digital ulcers in systemic sclerosis.⁵ Botulinum toxin injection also improved Raynaud's phenomenon and digital ulcers in a pilot study.⁶ Injecting botulinum toxin into the neurovascular bundle of the palm can attenuate vasospasm by blocking hyperactive vascular responses.⁶

In the present case, the digital ulcers combined with Raynaud's phenomenon were significantly improved after applying a combination of botulinum toxin injection and oral ERA. Although the pathophysiology of skin ulceration in anti-MDA5-Ab-positive DM has been not fully elucidated, the present case

provides new insight into the possible mechanism of abnormal dermatologic manifestation in anti-MDA5-Ab-positive DM. Furthermore, we suggest novel treatment options for digital ulcers in anti-MDA5-Ab-positive DM patients. A future larger scale study is needed to confirm the therapeutic effects of botulinum toxin injection and ERA in dermatologic manifestations of anti-MDA5-Ab-positive DM patients.

Author Contributions

Conceptualization: Kyomin Choi. Investigation: Hong Ki Min, Kyomin Choi. Supervision: Hae-Rim Kim, Jeeyoung Oh, Sang-Heon Lee. Visualization: Sung-Hye Park. Writing—original draft: Hong Ki Min. Writing—review & editing: Kyomin Choi.

ORCID iDs

Hong Ki Min	https://orcid.org/0000-0003-1147-1046
Hae-Rim Kim	https://orcid.org/0000-0002-1911-6236
Sang-Heon Lee	https://orcid.org/0000-0002-7539-9330
Sung-Hye Park	https://orcid.org/0000-0002-8681-1597
Jeeyoung Oh	https://orcid.org/0000-0002-0378-2947
Kyomin Choi	https://orcid.org/0000-0001-9730-3363

Conflicts of Interest

The authors have no potential conflicts of interest to disclose.

REFERENCES

1. Selva-O'Callaghan A, Pinal-Fernandez I, Trallero-Araguás E, Milisen-da JC, Grau-Junyent JM, Mammen AL. Classification and management of adult inflammatory myopathies. *Lancet Neurol* 2018;17:816-828.
2. 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.
3. Greenberg SA. Dermatomyositis and type 1 interferons. *Curr Rheumatol Rep* 2010;12:198-203.
4. Abe Y, Matsushita M, Tada K, Yamaji K, Takasaki Y, Tamura N. Clinical characteristics and change in the antibody titres of patients with anti-MDA5 antibody-positive inflammatory myositis. *Rheumatology (Oxford)* 2017;56:1492-1497.
5. Hughes M, Herrick AL. Digital ulcers in systemic sclerosis. *Rheumatology (Oxford)* 2017;56:14-25.
6. Motegi S, Yamada K, Toki S, Uchiyama A, Kubota Y, Nakamura T, et al. Beneficial effect of botulinum toxin A on Raynaud's phenomenon in Japanese patients with systemic sclerosis: a prospective, case series study. *J Dermatol* 2016;43:56-62.