Case Report
Olgu Sunumu

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Anti-MDA5 antibody-positive dermatomyositis with severe cutaneous ulcers

Şiddetli kutanöz ülserlerle seyreden anti-MDA5 pozitif dermatomiyozit

Büşra Demirbağ Gül, Nilgün Şentürk, Deniz Bayçelebi*, Levent Yıldız*

Ondokuz Mayıs University Faculty of Medicine, Department of Dermatology; *Department of Pathology, Samsun, Turkey

Abstract

Anti-melanoma differentiation-associated protein 5 (anti-MDA5) antibody-positive dermatomyositis (DM) is a subtype of DM described recently. It has atypical features compared with classical DM, such as cutaneous ulcers, interstitial lung disease (ILD), arthritis, and less muscle involvement. We presented a patient diagnosed with anti-MDA5 antibody-positive DM with severe cutaneous ulcers, whose symptoms started after an electrical injury trauma. The patient was a 33-year-old man who was admitted to our department with skin rash, arthralgia, and weakness developing during the last 2 months. In his medical history, he sustained a low-voltage electrical injury 1 month ago. He was diagnosed with DM according to the physical examination, laboratory, and radiological findings and cutaneous histopathology. Treatment with oral administration of prednisolone 1 mg/kg/day and intravenous administration of immunoglobulin 2 g/kg/day was initiated. At the start of symptom improvement, the prednisolone dose was gradually tapered. At the third visit, his condition deteriorated, presenting with cutaneous and mucosal ulcers. At this point, the extended myositis panel was sent, and anti-MDA5 antibody was detected. High-resolution computed tomography revealed peripheral intralobular reticular opacities on both lungs, which indicated ILD in the early stage. Therefore, intravenous administration of cyclophosphamide 1000 mg once a month was added to steroid and intravenous immunoglobulin. His treatment continued with dramatic improvement. Anti-MDA5 antibody-positive DM has a significant risk of developing rapidly progressive ILD, therefore diagnosing timely is critical for prognosis.

Keywords: Cutaneous ulcers, dermatomyositis, anti-MDA 5 antibody

Öz

Anti-melanom farklılaşması ile ilişkili protein 5 (anti-MDA5) antikoru pozitif dermatomiyozit (DM), son zamanlarda tanımlanmış bir DM alt tipidir. Klasik DM ile karşılaştırıldığında kutanöz ülserler, interstisyel akciğer hastalığı (İAH), artrit ve daha az kas tutulumu görülmesi gibi atipik özelliklere sahiptir. Burada, semptomları elektrik travması sonra başlayan, şiddetli kutanöz ülserli, anti-MDA5 antikoru pozitif DM tanısı konan bir hastayı sunduk. Otuz üç yaşında erkek hasta son iki aydır gelişen deri döküntüsü, artralji, halsizlik şikayetleri ile kliniğimize başvurdu. Özgeçmişinde bir ay önce düşük voltajlı elektrik travması geçirdiği öğrenildi. Fizik muayene, laboratuvar, radyoloji bulguları, deri histopatolojisine göre DM tanısı konuldu. Oral prednizolon 1 mg/kg/gün ve intravenöz immünoglobulin 2 g/kg/ay tedavisi başlandı. Başlangıçta semptomlar düzeldiği için prednizolon dozu kademeli olarak azaltıldı. Üçüncü vizitte hasta kutanöz ve mukozal ülserlerle tarafımıza başvurdu. Bu noktada, genişletilmiş miyozit antikor paneli testi gönderildi ve anti-MDA5 antikorunun varlığı tespit edildi. Yüksek çözünürlüklü bilgisayarlı tomografide, her iki akciğerde erken İAH anlamına gelen periferik intralobüler retiküler opasiteler görüldü. Bu nedenle steroid ve intravenöz immünoglobulin tedavsine ek olarak ayda bir kez 1000 mg intravenöz siklofosfamid eklendi. Hastanın tedavisi dramatik bir iyileşme ile birlikte devam ediyor. Anti-MDA5 pozitif DM, hızlı ilerleyen İAH geliştirme açısından önemli bir riske sahiptir, bu nedenle zamanında teşhis, prognoz için kritik öneme sahiptir.

Anahtar Kelimeler: Kutanöz ülserler, dermatomiyozit, anti-MDA 5 antikoru

Address for Correspondence/Yazışma Adresi: Büşra Demirbağ Gül MD, Ondokuz Mayıs University Faculty of Medicine, Department of Dermatology, Samsun, Turkey
Phone: +90 506 621 47 32 **E-mail:** busrademirbag@windowslive.com **Received/Geliş Tarihi:** 26.05.2022 **Accepted/Kabul Tarihi:** 08.11.2022
ORCID: orcid.org/0000-0003-3959-3977

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Introduction

Anti-melanoma differentiation-associated protein 5 (anti-MDA5) antibody-positive dermatomyositis (DM) is a recently described subtype of DM that is characterized by atypical features compared with classical DM, such as cutaneous ulcers, interstitial lung disease (ILD) with poor prognosis, and arthritis. Timely diagnosis is critical for prognosis because this subtype has a significant risk of developing rapidly progressive ILD. Herein, we described a patient with anti-MDA5 antibody-positive DM with severe cutaneous ulcers.

Case Report

The patient was a 33-year-old man who presented with skin rash, arthralgia, and weakness that developed 1 month before admission. He sustained a low-voltage electrical injury (250 V) 1 month before the initial symptom onset. Physical examination revealed an erythematous rash on the periorbital areas, elbows, knees, and dorsum of the metacarpophalangeal joints (MCPJ). His muscle strength in proximal muscle groups was 4/5. Laboratory examination revealed elevated transaminases [aspartate aminotransferase (AST), 159 U/L; alanine aminotransferase (ALT), 134 U/L], ferritin (554 ng/mL), and red blood distribution width [Red blood cell distribution width (RDW): 14.4%]. Other inflammatory markers, creatinine phosphokinase (CPK), lactate dehydrogenase (LDH), aldolase, standard myositis panel, and chest X-ray imaging results were within normal limits. Electromyography (EMG) and musculoskeletal magnetic resonance imaging (MRI) of the femoral muscles showed evidence of myositis. Muscle biopsy obtained from the quadriceps muscle had normal histomorphological features. Skin biopsy from the elbow showed epidermal atrophy, vacuolization in basal keratinocytes, and mucin deposition in the papillary dermis (Figure 1, 2). Liver elastography revealed liver fibrosis without cirrhosis, and a liver biopsy showed normal histopathological features. With these findings, the diagnosis of DM was established, and treatment with oral administration of prednisolone 1 mg/kg/day was initiated. Adjuvant immunosuppressive agents were not preferred because of elevated transaminases; thus, intravenous immunoglobulin (IVIg) was administered at 2 g/kg monthly. As the symptoms improved, the prednisolone dose was gradually tapered. Over the ensuing 3 months, he was admitted for IVIg infusion every month. At the 4th visit, his condition deteriorated, presenting with cutaneous ulcers, nasal regurgitation, and weight loss. He denied respiratory symptoms. On examination, the patient was cachectic and had normal vital signs. Deep cutaneous ulcers were detected on the elbows, sacral area, knees, and dorsum of the MCPJ. Non-scarring alopecia was noted on the occipital area, and palmar papules on the lateral borders of the fingers were observed. On oral examination, a 5 mm diameter perforation was found on the pharynx posterior wall. At this point, the extended myositis panel was sent, and anti-MDA5 antibody was detected. He had elevated ferritin (1200 ng/mL) and RDW (20.2%) and normal inflammatory markers, AST, ALT, CPK, and LDH. Chest tomography revealed peripheral intralobular reticular opacities on both lungs, which indicated ILD in the early stage. In addition to IVIg and increased steroid dose, intravenous pulse cyclophosphamide 1000 mg monthly was initiated. Treatment with oral prednisolone tapering, IVIg 2 g/kg/monthly, and intravenous cyclophosphamide at 1000 mg/month were continued for 6 months, and satisfactory symptom improvement was achieved (Figure 3, 4).

Discussion

Anti-MDA5 antibody-positive DM, which has more prevalent ILD and distinctive cutaneous findings such as ulcers, alopecia, and palmar papules, is a recently described subtype of DM.

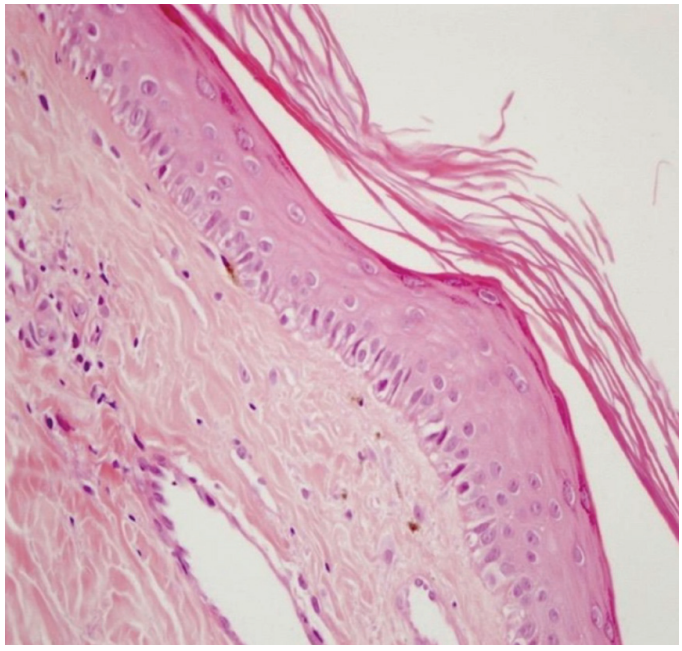

Figure 1. Epidermal atrophy, vacuolization in basal keratinocytes, and mucin deposition in the papillary dermis

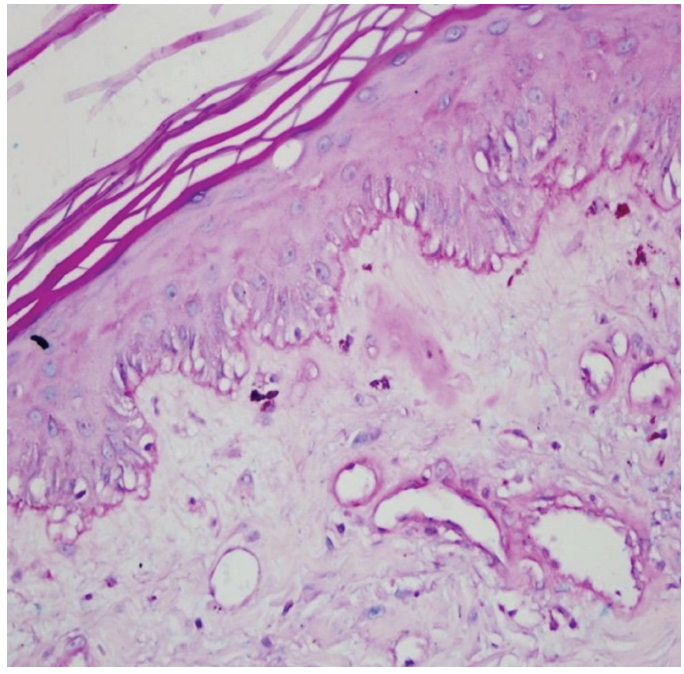

Figure 2. Epidermal atrophy, vacuolization in basal keratinocytes, and mucin deposition in the papillary dermis

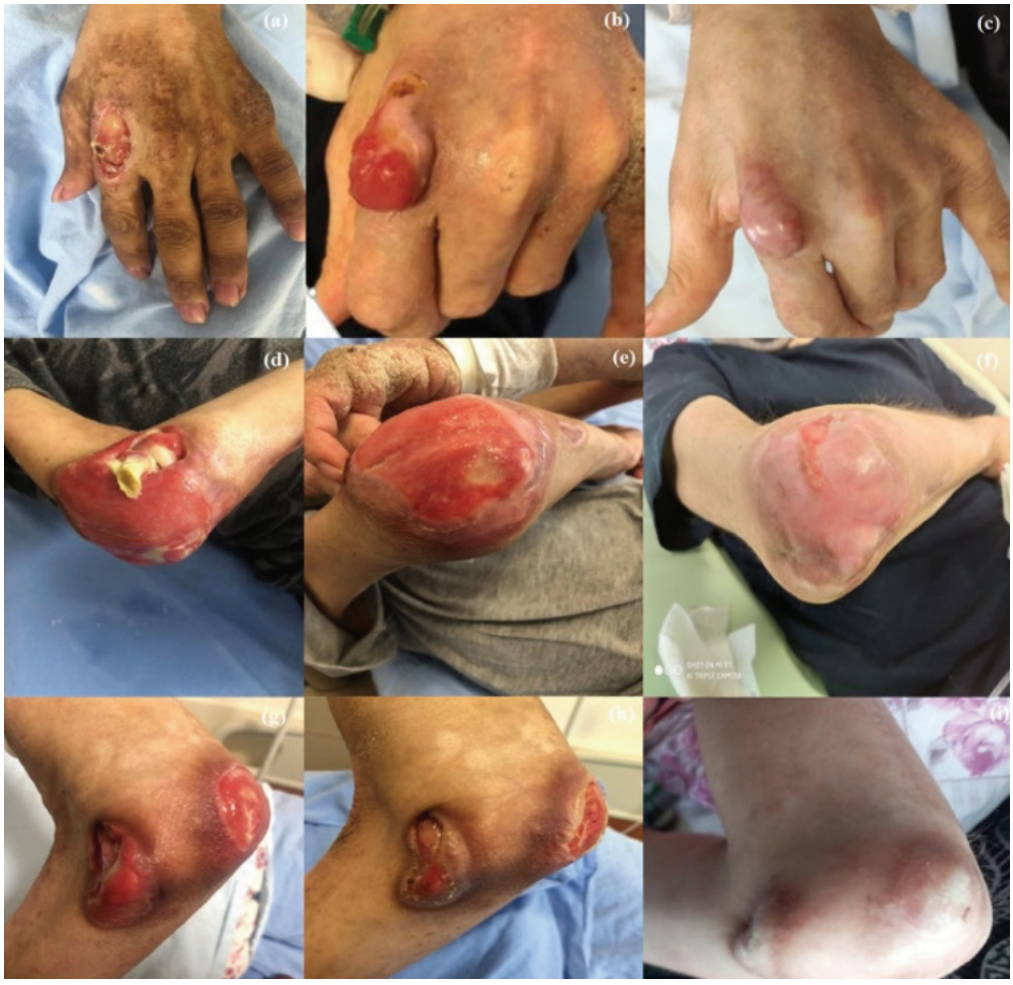

Figure 3. (a-c) Ulcer on the right hand at 4th, 6th, and 9th months, respectively. **(d-f)** Ulcer on the right elbow at the 4th, 6th, and 9th months, respectively. **(g-i)** Ulcer on the left elbow at the 4th, 6th, and 9th months, respectively

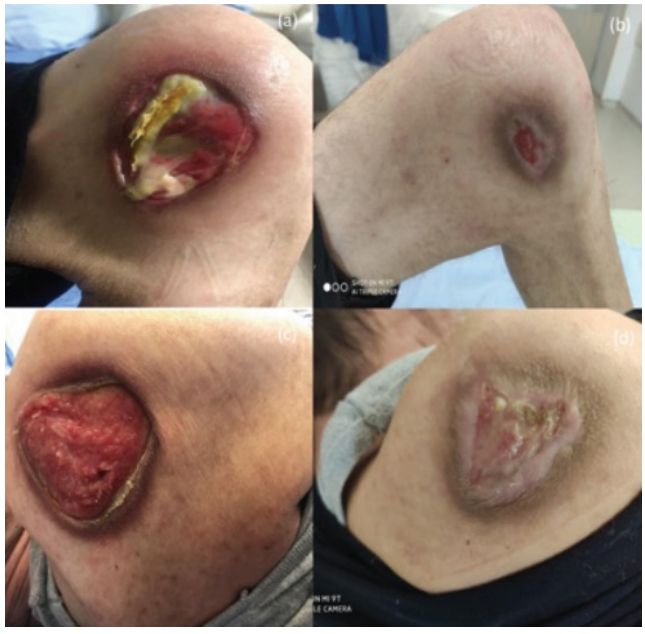

Figure 4. (a, b) Ulcer on the medial surface of the left knee at the 4th and 6th months, respectively. **(c, d)** Ulcer on the right shoulder at the 4th and 6th months, respectively

MDA5 is a member of retinoic acid-inducible gene I-like receptors (RLRs), which are responsible for innate immune response by recognizing the intracellular viral genome, especially viral RNA derivations. It induces type 1 interferon (IFN), IFN-stimulated genes, and proinflammatory cytokines[1]. The expressions of RLRs are also induced by type 1 IFNs to provide an effective immune response[2]. The pathogenesis of the antibody development to MDA5 is unclear. Viral infections may be triggering factors because of the role of MDA5 in the innate immune response. Uncontrolled viral infection or severe type 1 IFN-induced inflammation may cause increased susceptibility to tissue damage, and this process may lead to the development of autoimmunity[3]. In our case, the symptoms began 1 month after an electrical injury, which may be the triggering factor. Electrical injuries cause tissue damage including electroporation of cell membranes, cell swelling and rupture, cell fusion, electroconformational change of ion channels and pumps, thermal denaturation of proteins, DNA, and RNA, and lipid peroxidation[4]. These effects can result in cell disintegration and release of cytosolic contents. Since MDA5 has a cytosolic structure, following these damage processes, MDA5 may be released and become recognizable by the immune system. The disruption of the balance between proinflammatory and non-inflammatory states due to electrical trauma might have played a role. Ultimately, these mechanisms may lead to an autoantibody formation.

In the presented case, the patient had skin findings of classic DM for the first 3 months. In the fourth month, deep severe cutaneous ulcers, palmar papules, alopecia, and perforation on the pharynx had begun. We attributed this deterioration to the reduction of effective immunosuppression because of the decreasing steroid dose. While mild proximal muscle weakness and EMG-MRI findings were consistent with muscle involvement, CPK, LDH, aldolase levels, and muscle biopsy results were unremarkable. Although the patient's EMG and skeletal MRI findings suggest likely myositis, muscle involvement of DM could not be clearly shown because electrical trauma could also lead to muscle damage. Our patient also had elevated AST and ALT levels. Elevated transaminases with normal muscle enzymes suggest liver pathology. Nagashima et al.[5] described that liver dysfunction is an extramuscular manifestation in patients with clinically amyopathic DM who are anti-MDA5 antibody-positive. Elevated transaminases, fibrosis on liver elastography, and regression of transaminases after treatment showed that the liver dysfunction in this patient was a manifestation of anti-MDA5 antibody-positive DM.

Studies have shown that serum ferritin level correlates with MDA5-positive DM disease activity, especially with ILD[6]. Similarly, the patient's ferritin level was above 1000 IU/L, which correlated with skin symptoms. On consecutive visits, reduction of ferritin levels correlated with the improvement of cutaneous ulcers. Moreover, the patient's RDW tended to increase when the disease was active. Studies have proven that RDW is increased in autoimmune diseases such as rheumatoid arthritis, systemic lupus erythematosus, and inflammatory myositis[7]. Over the ensuing months, the RDW decreased with treatment, similarly with ferritin levels (Figure 5). Therefore, RDW may be used for evaluating disease activity in anti-MDA5-positive DM, similar to ferritin.

In the present case, anti-MDA5 antibody was not initially measured because of health insurance regulations. It was detected when there was a high clinical suspicion of anti-MDA5 antibody-positive DM. In the future, routine testing for MDA5 antibody in selected patients with DM may benefit the prognosis.

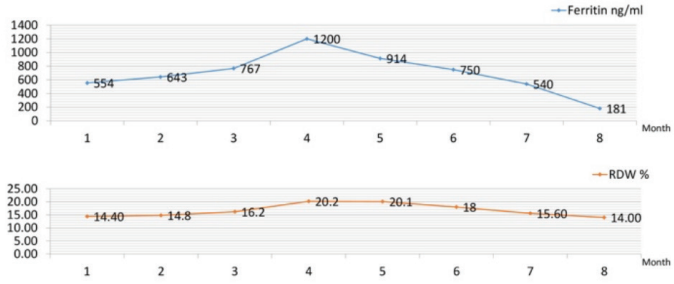

Figure 5. Changes in red blood distribution width and ferritin values after the addition of cyclophosphamide to the treatment at the 5th month

This case was remarkable for disease initiation after electrical injury, development of predominantly severe cutaneous ulcers, and dramatic response to a combination of oral corticosteroids, IV cyclophosphamide, and IVIg.

Ethics

Informed Consent: It was obtained.

Peer-review: Externally peer-reviewed.

Authorship Contributions

Surgical and Medical Practices: B.D.G., N.Ş., D.B., L.Y., Concept: B.D.G., N.Ş., Design: B.D.G., N.Ş., Data Collection or Processing: B.D.G., D.B., L.Y., Analysis or Interpretation: B.D.G., N.Ş., Literature Search: B.D.G., D.B., Writing: B.D.G., N.Ş., D.B., L.Y.

Conflict of Interest: No conflict of interest was declared by the authors.

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References

1. Dixit E, Kagan JC: Intracellular pathogen detection by RIG-I-like receptors. Adv Immunol 2013;117:99-125.
2. Kang DC, Gopalkrishnan RV, Lin L, Randolph A, Valerie K, Pestka S, et al.: Expression analysis and genomic characterization of human melanoma differentiation associated gene-5, mda-5: a novel type I interferon-responsive apoptosis-inducing gene. Oncogene 2004;23:1789-1800.
3. Chaisson NF, Paik J, Orbai A, Casciola-Rosen L, Fiorentino D, Danoff S, et al.: A novel dermato-pulmonary syndrome associated with MDA-5 antibodies: report of 2 cases and review of the literature. Medicine (Baltimore) 2012;91:220-8.
4. Tsong TY: Understanding the cellular and molecular basis of electrical shock. Ann N Y Acad Sci 1999;888:150-2.
5. Nagashima T, Kamata Y, Iwamoto M, Okazaki H, Fukushima N, Minota S: Liver dysfunction in anti-melanoma differentiation-associated gene 5 antibody-positive patients with dermatomyositis. Rheumatol Int 2019;39:901-9.
6. Gono T, Kawaguchi Y, Ozeki E, Ota Y, Satoh T, Kuwana M, et al.: Serum ferritin correlates with activity of anti-MDA5 antibody-associated acute interstitial lung disease as a complication of dermatomyositis. Mod Rheumatol 2011;21:223-7.
7. Hu ZD: Red blood cell distribution width: a promising index for estimating activity of autoimmune disease. J Lab Precis Med 2016;1:4.