

Single Case

# Acral Cutaneous Ulcerations and Livedo Reticularis with Rapidly Progressive Interstitial Lung Disease in Anti-MDA5 Antibody-Positive Classical Dermatomyositis

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## Keywords

Cutaneous ulceration · Livedo reticularis · Dermatomyositis

## Abstract

Rapidly progressive interstitial lung disease (RP-ILD) and its distinctive cutaneous features are highly associated with the presence of anti-melanoma differentiation-associated gene 5 (anti-MDA5) antibody in patients with dermatomyositis (DM), leading to a poor prognosis. We describe the case of a 25-year-old man who developed progressive proximal muscle weakness with RP-ILD and had unusual cutaneous findings (cutaneous ulcerations and livedo reticularis) accompanied by classical cutaneous features (heliotrope rash, Gottron's papules, Gottron's sign, and flagellate erythema). Blood test was positive for anti-MDA5 antibody. He was treated with intravenous corticosteroids and immunoglobulin, but passed away due to respiratory failure within 1 month after admission. Our case highlights that the presence of cutaneous ulcerations and livedo reticularis, in addition to RP-ILD, are useful clinical clues that may aid in the

detection of anti-MDA5 antibody, early initiation of combined immunosuppressants, and prognosis prediction in patients with classical DM.

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## Introduction

Dermatomyositis (DM) is a systemic autoimmune disease typically characterized by chronic inflammation of muscle and skin. However, 5–46% of patients with DM can also develop interstitial lung disease (ILD) [1]. Diagnosis is based on clinical manifestations of characteristic cutaneous eruption (heliotrope sign, Gottron's papules, and Gottron's sign) with or without proximal muscle weakness and supportive laboratory findings including electromyographic or histopathological muscle findings, and those regarding muscle enzymes or myositis-specific antibodies (MSAs). Although the estimated rates of MSA positivity in DM range from just 20 to 50%, MSA tests have increasingly been used to help diagnose DM, predict prognosis, and guide treatment [2]. However, the presence of MSAs usually correlates with that of distinct clinical features. We report a case of classical DM presenting with rapidly progressive ILD (RP-ILD) and unusual cutaneous features (ulcerations on Gottron's papules and the palmar surfaces of the interphalangeal joints and livedo reticularis on the palmar surfaces of the index fingers) associated with anti-melanoma differentiation-associated gene 5 (anti-MDA5) antibody.

## Case Report

A 25-year-old healthy Thai man presented with progressive dyspnea for 1 month. Four months earlier, the patient had developed generalized myalgia without clinical weakness that was predominant on both thighs (pain score 7/10) and a low-grade fever. Two months later, the fever persisted and he complained of difficulty climbing stairs. He had occasional knee pain on both sides and weight loss from 65 to 60 kg in 3 months. One month later, he developed rapidly progressive dyspnea and noticed a new-onset periorbital rash, which brought him to the hospital.

Vital signs on admission were temperature of 36.7°C, blood pressure of 115/75 mm Hg, pulse rate of 119 beats/min, respiratory rate of 30 breaths/min, and severe hypoxemia (SpO<sub>2</sub> 74% in room air). Physical examination revealed erythematous to violaceous patches on the periorbital areas (heliotrope rash), red to violaceous papules (Gottron's papules) with overlying ulcerations and crusts on the right 3rd metacarpophalangeal joint and 4th proximal interphalangeal joint, ill-defined violaceous erythema (Gottron's sign) on the left 3rd metacarpophalangeal joint, tender erythematous papules, and ulcerations on the palmar surfaces of the distal interphalangeal joints of both hands and medial aspect of the index fingers. Livedo reticularis was also detected on the palmar surfaces of the index fingers of both hands, and erythematous linear plaques (flagellate erythema) were noticed on both inner thighs (Fig. 1). Mechanic's hands were not found. Chest auscultation was notable for bilateral basal lung crepitation. He had bilateral proximal muscle weakness grade IV/V at both the upper and lower extremities. No signs of arthritis were detected. Other findings were unremarkable.

Laboratory investigations showed mild anemia (Hb 9.1 g/dL), a white blood cell count of 10,370/μL (neutrophils 85%, lymphocytes 8%, monocytes 4%, eosinophils 3%), a C-reactive protein level of 3.53 mg/dL, and an erythrocyte sedimentation rate of 68 mm/h. Creatine kinase and aspartate aminotransferase were high at 505 mg/dL and 105 IU/L, respectively.

Alanine aminotransferase was normal (20 IU/L). The anti-nuclear antibody titer was 1:80 (fine speckle type and cytoplasmic pattern), and anti-Ro-52 was positive. Anti-MDA5 antibody was positive, whereas anti-Jo-1, anti-Mi-2, and anti-SRP antibodies as well as other myositis panels were negative which were detected by Western blot.

An anteroposterior chest X-ray showed bilateral interstitial infiltration at both lungs. A high-resolution CT scan of the chest revealed multifocal areas of ground glass attenuation and alveolar opacity throughout the lung parenchyma and predominately at the peripheral and peribronchiolar regions (Fig. 2). Electromyographic findings suggested inflammatory myositis. Histopathological findings from the right 3rd knuckle revealed interface changes with sparse inflammatory cell infiltrate (Fig. 2).

The patient was diagnosed with RP-ILD with anti-MDA5 antibody-positive classical DM. He was initially treated with intravenous hydrocortisone (300 mg/day) and 125 g of intravenous immunoglobulin (0.4 g/kg/day) divided over 5 days due to impending respiratory failure. However, his condition deteriorated. He developed new-onset fever on the 7th day after admission and a chest X-ray showed progressive alveolar infiltration. Meropenem was administered intravenously at a dose of 1 g every 8 h. Bronchoalveolar lavage was performed and bronchoalveolar lavage fluid cultures were negative for microorganisms. Pathological trans-bronchial biopsy results revealed benign bronchial epithelium with fibrinous material and no malignancy. Dexamethasone was administered intravenously at a dosage of 20 mg per day in addition to the patient's existing treatment regimen. However, his status progressed towards respiratory failure, and he required ventilator support. He died due to respiratory failure on day 22.

## Discussion

ILD is the most common systemic manifestation in DM and is commonly associated with high mortality rates. It can develop in various myositis subtypes, but is most highly associated with antisynthetase syndrome and anti-MDA5 antibody-positive DM. Antisynthetase syndrome is characterized by the presence of antisynthetase antibodies that are directed against aminoacyl-tRNA synthetase enzymes (ARS antibodies) and a group of symptoms that include ILD, myositis, polyarthritis, fever, Raynaud phenomenon, and mechanic's hands [3]. Among the eight specific anti-ARS antibodies (anti-Jo-1, anti-PL7, anti-PL12, anti-EJ, anti-OJ, anti-KS, anti-Zo, and anti-Ha/YRS) that share some clinical features, anti-Jo-1 is the one most commonly associated with ILD and mechanic's hands [4] and is also highly associated with myositis [5]. However, other anti-ARS antibodies are also associated with ILD. The clinical presentation of ILD in patients with anti-synthetase syndrome can range from no symptoms to acute respiratory failure, requiring a combination of corticosteroids and immunosuppressive agents [6]. However, anti-synthetase syndrome-associated ILD responds better to therapy and has a higher survival rate than anti-MDA5-associated ILD [7].

Anti-MDA5 antibody-positive DM is a unique DM subtype characterized by distinct cutaneous and systemic manifestations, of which ILD is the most common systemic complication. Anti-MDA5 antibody is associated with an increased the risk of developing fatal acute-onset ILD and RP-ILD, especially in Asian populations, and is highly associated with clinically amyopathic DM [2, 8]. However, anti-MDA5 antibody is also present in classical DM patients [9]. A previous study reported that 79% of anti-MDA5 antibody-positive DM patients developed RP-ILD, 50% of whom died from respiratory failure, and that 82% of anti-MDA5 antibody-positive DM patients were diagnosed with clinically amyopathic DM [10]. Apart from

typical cutaneous manifestations, the most common cutaneous signs of anti-MDA5 antibody-positive DM are cutaneous ulceration and painful palmar papules, with an estimated prevalence of 40–82% and 20–60%, respectively [9]. Cutaneous ulceration commonly occurs on Gottron's papules, the elbows and knees, and in periungual areas [2, 9, 11]. Recent studies have shown that presence of anti-MDA5 antibodies and cutaneous ulceration are strong risk factors for RP-ILD [12, 13]. Palmar papules are usually painful and commonly occur on the metacarpophalangeal and interphalangeal joint creases of the palms [9]. These findings are thought to be due to vasculopathy [14, 15]. Other findings that have been reported in anti-MDA5 antibody-positive DM patients are nonscarring alopecia, panniculitis, mechanic's hand, and oral ulcers [2, 9].

Our patient presented with clinical rapidly progressive dyspnea within 1 month with clinical signs of impending respiratory failure and severe hypoxemia, which is compatible with RP-ILD. This was confirmed by high-resolution CT of the chest. The patient also had proximal muscle weakness with elevated muscle enzymes and typical cutaneous manifestations that were compatible with classical DM. The differential diagnosis included anti-MDA5 antibody-positive DM and antisynthetase syndrome. In addition to the typical cutaneous features of DM, our patient also had cutaneous ulcerations and livedo reticularis on the index fingers, with absence of mechanic's hand and Raynaud phenomenon. These findings led to an initial diagnosis of anti-MDA5 antibody-positive DM, which was later confirmed by a blood test that was positive for anti-MDA5 antibody. Other systemic symptoms that have been reported in anti-MDA5 antibody-positive DM patients, such as arthralgia and fever, were also present in our patient. We performed a skin biopsy at the right 3rd knuckle near the ulceration to identify its pathology, but the histopathological results showed only interface changes and sparse inflammatory cell infiltrate without vascular or perivascular abnormality.

RP-ILD accompanied by anti-MDA5 antibodies is an aggressive form of DM that has a poor prognosis, especially in the presence of high anti-MDA5 autoantibody titers. Treatment of this condition is challenging and there is no standard regimen. Typically, RP-ILD requires initial high-dose glucocorticoid combined with other immunosuppressive agents such as cyclophosphamide, rituximab, and calcineurin inhibitors (including cyclosporin A and tacrolimus) [16, 17]. A recent multicenter prospective study demonstrated that a combination of immunosuppressive drugs, consisting of high-dose glucocorticoid, tacrolimus, and intravenous cyclophosphamide, was significantly more effective in patients with anti-MDA5-positive DM with ILD than step-up treatment (high-dose glucocorticoid and stepwise addition of immunosuppressive drugs) [18]. Although our patient received a combination of high-dose intravenous corticosteroids and immunoglobulin, his condition worsened, and he passed away due to respiratory failure.

In conclusion, we describe the case of a patient with anti-MDA5 antibody-positive classical DM who developed RP-ILD and had cutaneous ulceration and livedo reticularis on both hands. The cutaneous ulceration and livedo reticularis were crucial clues that prompted clinicians to test for anti-MDA5 antibody and initiate early aggressive treatment for RP-ILD associated with classical DM.

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### Statement of Ethics

This case report was reviewed and approved by the Ethics Committee in Human Research, Khon Kaen University, Thailand (HE 621535). The patient's parents gave their written informed consent for publication of the case, including images. The authors have no ethical conflicts to disclose.

### Disclosure Statement

The authors declare no conflicts of interest.

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### Author Contributions

All named authors meet the International Committee of Medical Journal Editors criteria for authorship for this article, take responsibility for the integrity of the work as a whole, and gave their approval for this version to be published.

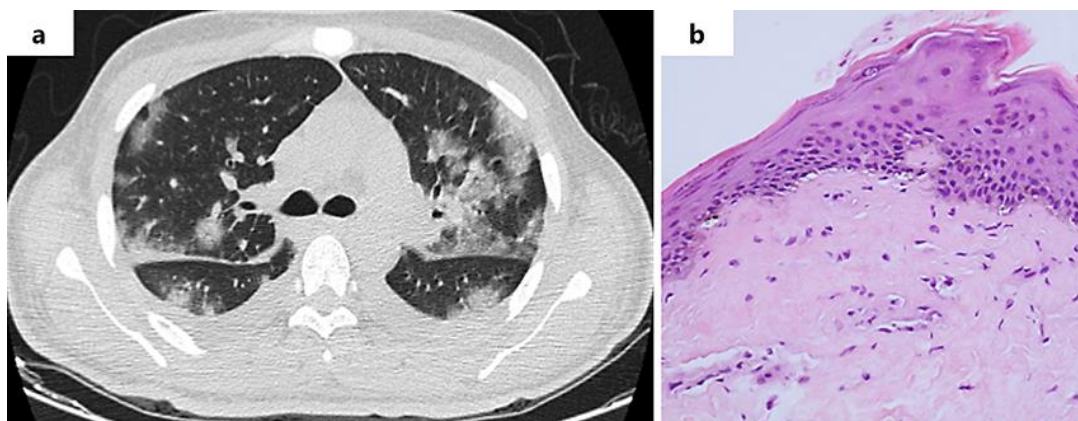
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**Fig. 1.** **a** Heliotrope rash on the periorbital areas. **b, c** Painful, erythematous papules and ulcerations on the palmar surfaces of the distal interphalangeal joints of both hands and medial aspects of the index fingers. Livedo reticularis was also noticed on the index fingers of both hands (arrows). **d** Flagellate erythema on both inner thighs. **e** Gottron's sign on the left 3rd metacarpophalangeal joint. **f** Gottron's papules with central ulcerations and crusts on the right 3rd metacarpophalangeal joint and 4th proximal interphalangeal joint.



**Fig. 2.** **a** High-resolution CT of the chest showed multifocal areas of ground-glass attenuation. **b** A skin biopsy specimen from the right 3rd knuckle showed focal interface changes with sparse inflammatory cell infiltrate (hematoxylin and eosin staining, original magnification  $\times 100$ ).