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【 CASE REPORT 】

# Fatal Thrombotic Microangiopathy and Posterior Reversible Encephalopathy Syndrome in a Patient with Anti-melanoma Differentiation-associated Gene 5 Antibody-positive Dermatomyositis

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**Abstract:**

A 56-year-old woman presented with dermatomyositis positive for anti-melanoma differentiation-associated gene 5 antibody. No interstitial lung disease was detected. Despite treatment with methylprednisolone pulse therapy and cyclosporine, dysphagia developed. Furthermore, the presence of thrombocytopenia, elevated lactate dehydrogenase levels, and an undetectable haptoglobin level suggested the possibility of thrombotic microangiopathy (TMA). Disturbed consciousness developed shortly after TMA onset, and brain magnetic resonance imaging revealed hyperintensity lesions in the bilateral basal ganglia, thalami, and brainstem. The patient was diagnosed with atypical posterior leukoencephalopathy syndrome before dying of heart failure later that day. In conclusion, early TMA recognition and prompt intensive treatment are critical in such cases.

**Key words:** hemophagocytic syndrome, hemophagocytic lymphohistiocytosis, interstitial lung disease, thrombotic thrombocytopenic purpura

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## Introduction

Anti-melanoma differentiation-associated gene 5 (anti-MDA5) antibody-positive dermatomyositis (DM) accounts for 11-60% of cases of DM in Asian patients. Among such patients, more than 90% also suffer from interstitial lung disease (ILD), which follows a rapidly progressive course in 33-71% of patients. Furthermore, approximately half of all cases of ILD result in death (1-5). Intensive immunosuppressive therapy consisting of a combination of glucocorticoids, cyclophosphamide, and calcineurin inhibitors (CNIs) is typically required to treat rapidly progressive ILD (6).

Posterior reversible encephalopathy syndrome (PRES) is a neurological disorder characterized by various neurological symptoms, including headache, loss of vision, seizure, mental disorder, disturbance of consciousness, and focal neurological symptoms (7, 8). During neuroimaging, patients with PRES typically show reversible brain edema in the bilateral parieto-occipital regions as well as the posterior frontal, temporal, cerebellar, basal ganglia, and brainstem locations (8). While connective tissue diseases, such as systemic lupus erythematosus (SLE), vasculitis, systemic sclerosis, and Sjögren's syndrome, can cause PRES, DM is rarely the underlying condition (8-10).

Thrombotic thrombocytopenic purpura (TTP), a phenotype of thrombotic microangiopathy (TMA), is a potential cause of PRES (11, 12). Furthermore, connective tissue diseases are recognized as a cause of secondary TMA. Although rare, there have been reports of patients with both DM and TMA (13).

We herein report a patient with DM who was positive for anti-MDA5 antibody and complicated with both fatal TMA and PRES.

## Case Report

A 56-year-old woman was transferred to our hospital for

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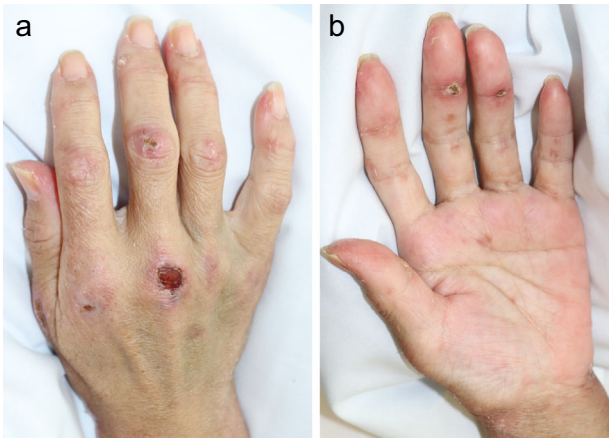


**Figure 1. The patient's hand is shown. (a) Gottron's signs on the surface of the finger joints. There were skin ulcers over the metacarpophalangeal and proximal interphalangeal joints, and around the periungual area. (b) Palmar aspect of the hand. Skin ulcers were present over the palmar side of the finger joints in the third and fourth digits, indicating inverse Gottron's signs.**

the treatment of DM. The patient developed facial rash and hand edema five months prior to admission, whereas symptoms of a fever, facial and lower leg edema, deteriorating rash, exertional dyspnea, and muscle weakness had arisen only three weeks prior. She was diagnosed with DM by a physician due to the presence of Gottron's sign and muscle weakness. Treatment with prednisolone (PSL) 20 mg/day began shortly before referral.

Upon a physical examination, the patient showed facial erythema, Gottron's signs of the bilateral elbows, Gottron's signs on the bilateral dorsal hands, shawl sign, mechanic's hands, and skin ulcers around the periungual area (Fig. 1). Chest auscultation was normal. Myalgia was present in the thighs and lower legs, and arthralgia was noted in the elbows and wrists. Manual muscle testing revealed almost normal levels of muscle strength, except for the deltoid muscles. The following laboratory findings were recorded: leukocyte, hemoglobin, and platelet counts of 4,300/μL, 9.5 g/dL, and $8.0\times10^4$/μL, respectively; aspartate aminotransferase, alanine aminotransferase, lactate dehydrogenase (LDH), alkaline phosphatase, and γ-glutamyl transpeptidase levels of 532 U/L, 323 U/L, and 651 U/L (normal range, <216), 500 U/L (normal range, <322), and 264 U/L, respectively; creatine kinase and aldolase levels of 70 U/L and 27.8 U/L (normal range, <6.1), respectively; serum ferritin and Krebs von den Lungen-6 (KL-6) levels of 5,219 ng/mL (normal range, <114) and 1,271 U/mL (normal range, <500), respectively; C-reactive protein and immunoglobulin G levels of 0.01 mg/dL, and 2,066 mg/dL, respectively; and anti-MDA5 antibody positivity with an index value of 188 (normal range, <33). Antinuclear antibody, anti-double-stranded DNA antibody, anti-SSA antibody, MPO-ANCA, and PR3-ANCA findings were negative. A bone marrow examination revealed mild hemophagocytosis.

Computed tomography (CT) of the chest revealed no ILD. Transthoracic echocardiography showed a slightly reduced left ventricular function (ejection fraction, 53%). Short tau inversion recovery images taken during magnetic resonance imaging (MRI) of the thighs indicated the presence of a high-intensity lesion in the quadriceps femoris and biceps femoris muscles. Despite the previously given diagnosis of DM, a biopsy of the quadriceps femoris muscle did not reveal any myositis.

We began treatment with intravenous methylprednisolone (mPSL) pulse therapy (1 g/day for 3 days) followed by oral PSL and cyclosporine (CyA) doses of 40 mg/day (1 mg/kg) and 120 mg/day (3 mg/kg), respectively (Fig. 2). Although the serum ferritin and liver enzymes decreased, the platelet count also decreased sequentially, and myalgia continued. As the trough level of CyA was low (53 ng/mL), the dose was increased to 160 mg/day (4 mg/kg). On the 18th day after admission, we switched from oral administration of PSL and CyA to intravenous administration upon detecting worsening symptoms of dysphagia in the patient. On the 19th day, the oxygen saturation suddenly decreased to 90%. Chest CT revealed bilateral dorsal lung infiltration, suggesting either aspiration pneumonia or the emergence of ILD. KL-6 conversely decreased to 946 U/mL. The diagnosis of TMA was given based on the findings of thrombocytopenia, elevated LDH levels, and an undetectable serum level of haptoglobin.

We proposed a treatment with plasmapheresis, but the patient refused. Treatment with intravenous ampicillin/sulbactam (12 g/day) was initiated, after which intravenous cyclophosphamide (IVCY, 0.9 g, 0.75 g/$m^2$) was added to the treatment regimen. On the 21st day, the patient developed disturbance of consciousness, atrial fibrillation, and tachypnea. Serum ferritin and LDH levels further increased (7,667 ng/mL and 1,180 U/L, respectively), hemoglobin and platelet counts decreased (7.7 g/dL and $1.1\times10^4$/μL, respectively), and erythrocyte fragmentation was detected. CyA administration was discontinued as the trough level of CyA increased to 494 ng/mL. T2-weighted and fluid-attenuated inversion recovery images taken during brain MRI revealed high-intensity lesions in the bilateral basal ganglia, thalami, and brainstem (Fig. 3). Although the patient's blood pressure was nearly normal (systolic pressure of approximately 140 mmHg), the diagnosis of PRES was made, and another intravenous mPSL pulse was added to the treatment regimen. However, hypotension developed shortly after the pulse was administered. Transthoracic echocardiography revealed generalized myocardial hypomotility (ejection fraction, 30%) with asynergy of the anterior wall. The serum troponin T level was slightly elevated at 0.04 ng/mL (normal range, < 0.014).

Despite vasopressor therapy, the patient died a few hours later. Autopsy imaging using CT revealed no cerebral hemorrhaging or infarction. The activity level of a disintegrin and metalloproteinase with a thrombospondin type 1 motif, member 13 (ADAMTS13) was found to be normal, and

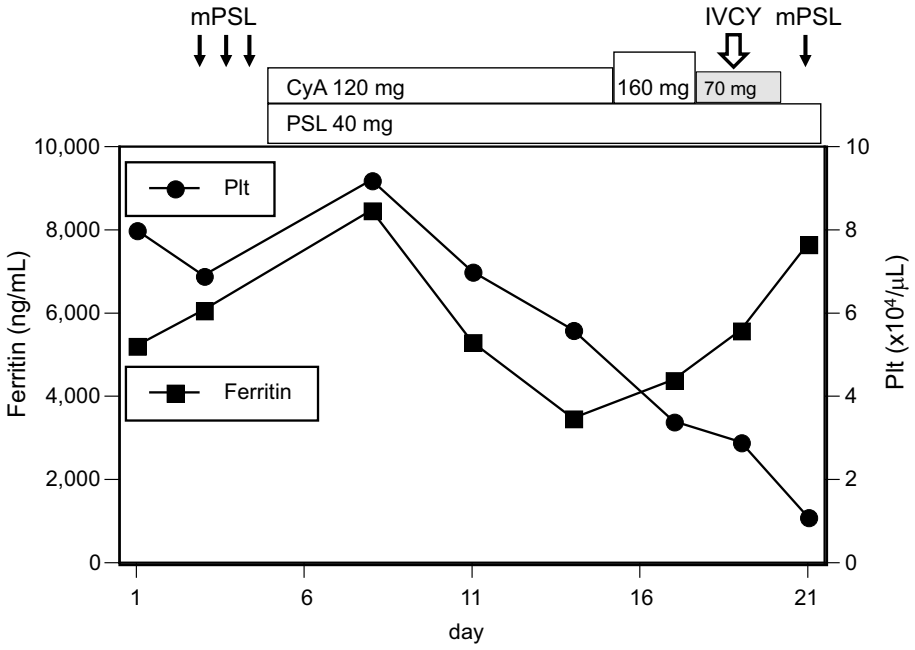


**Figure 2.** **Clinical course of the patient. CyA: cyclosporine, IVCY: intravenous cyclophosphamide, mPSL: methylprednisolone, Plt: platelet, PSL: prednisolone. The gray box indicates the intravenous administration of CyA.**

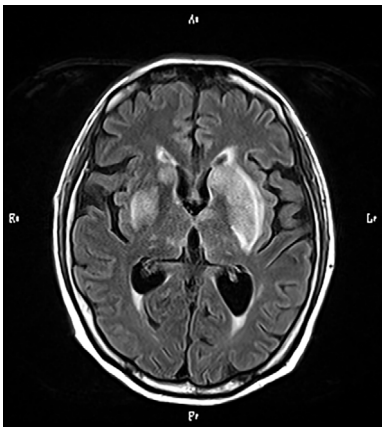

**Figure 3.** **Magnetic resonance imaging of the brain. Fluid-attenuated inversion recovery imaging revealed a hyperintensity lesion predominantly localized in the left basal ganglia and thalami.**

anti-ADAMTS13 antibody was not detected.

## Discussion

We herein report a patient with DM who was positive for anti-MDA5 antibody and developed TMA and PRES during intensive treatment. MRI revealed brain edema in the basal ganglia, thalami, and brainstem, which are atypical regions for PRES. The condition of the patient deteriorated rapidly after the development of TMA, resulting in death by heart failure shortly after the diagnosis of PRES was made.

Cases of DM complicated by PRES are rarely reported in the literature (10). We speculated that TMA was the most likely cause of PRES in the present case, as TMA was diagnosed shortly before the development of PRES. Previous reports of patients with SLE found that TMA, hemolytic anemia, and thrombocytopenia often coexisted once PRES began to develop (14). CyA has also been found to be a risk factor for PRES, but the incidence of PRES is reported to be less than 1% in patients undergoing organ transplantation (15, 16). However, CyA could not be ruled out as a causative drug, as PRES has been found to develop, irrespective of trough CyA levels (7, 16). Although cyclophosphamide has been reported as a rare cause of PRES, it is difficult to confirm the presence of a cause-and-effect relationship due to the implication of numerous other risk factors, such as renal involvement, hypertension, the use of glucocorticoids or other drugs, and underlying disease activity (17).

TMA is a rare complication of myositis that tends to develop when the disease activity of myositis is high (13). Similarly, the disease activity was elevated in our patient, as the serum ferritin levels increased along with the development of TMA. Previous studies have suggested that a correlation exists between serum ferritin levels and disease activity in patients positive for anti-MDA5 antibody (1). Although CNI is a potential cause of TMA, this association has only been reported in 0.12-3.3% of patients undergoing organ transplantation (18, 19). Thus, it seems unlikely that CyA was the cause of TMA in our patient. However, in cases where TMA is suspected, whether or not CNIs should be discontinued requires careful consideration. Although the activity of ADAMTS13 was found to be normal in the present patient, normal or subnormal levels of activity are often observed in patients with TMA associated with connective

tissue diseases, including DM (20).

The brain edema observed in the basal ganglia, thalami, and brainstem in the present case was atypical for PRES. Although the posterior portion of the parietal and occipital lobes are commonly involved in typical PRES, 2-6% of patients with PRES lack lesions in these areas (8, 21). These atypical patterns are referred to as "central-variant" PRES (22) and may be related to TTP or treatment with CyA (11, 22, 23). We were unable to confirm the reversibility of the brain edema in this case, as the patient died shortly after the diagnosis of PRES. However, no cerebral hemorrhaging or infarction was observed during autopsy imaging. Thus, the diagnosis of PRES may have been appropriate.

Myocardial involvement was the most probable direct cause of death in this patient, as echocardiography revealed generalized myocardial hypomotility with asynergy. Cardiac manifestations of TTP vary widely, with prior research reporting symptoms such as asymptomatic elevation of cardiac biomarkers, chest pains, arrhythmias, heart failure, myocardial infarction, and even sudden cardiac death (24). Among patients with myositis complicated by TMA, heart failure was found to be the cause of death in 3 out of 13 patients (13). However, the heart failure may have been an inherent manifestation of DM (25). Heart involvement is also common in patients with lupus as well as TMA (26). The prognosis also appears to be poor in patients with SLE who develop TMA and PRES (14).

In conclusion, we encountered a patient with anti-MDA5 antibody-positive DM complicated by both TMA and PRES. In addition to the finding of rapidly progressive ILD, the patient's TMA may have been a fatal complication of the anti-MDA5 antibody-positive DM observed in this case. If either TMA or PRES develops during the treatment of DM, it is critical to determine whether the complication is drug-induced or a consequence of the disease activity of DM per se. However, given the difficulty in discriminating these pathologies, the early recognition of TMA and prompt intensive treatment including plasmapheresis is critical.

**The authors state that they have no Conflict of Interest (COI).**

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