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【 CASE REPORT 】

Thrombotic Microangiopathy with Polymyositis/Dermatomyositis: Three Case Reports and a Literature Review

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Abstract:
Thrombotic microangiopathies (TMAs) rarely accompany polymyositis/dermatomyositis. We treated three patients with dermatomyositis combined with TMA. A literature review identified 13 previously reported cases. Exacerbation of myositis at the time of the TMA onset was observed in 62.5% of all patients, suggesting that the TMA onset may be associated with autoantibody production. We also found that cases of TMA with polymyositis/dermatomyositis often had a poor treatment response rate (37.5%). Furthermore, even if treatment was effective, the mortality rate associated with subsequent complications was high, and the survival rate was low (18.8%). Therefore, careful attention should be paid to patient management after TMA treatment.

Key words: polymyositis/dermatomyositis, thrombotic microangiopathies, thrombotic thrombocytopenic purpura, hemolytic-uremic syndrome

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Introduction

Polymyositis and dermatomyositis are connective tissue diseases (CTDs), and their principal clinical feature is symmetrical weakness of proximal muscle groups combined with elevated blood levels of muscle enzymes, particularly creatine phosphokinase (CK). The etiology is thought to be autoimmune in nature.

Thrombotic thrombocytopenic purpura (TTP) and hemolytic-uremic syndrome (HUS) were originally thought to be different diseases. Because both conditions involve organ damage caused by microvascular thrombosis, the diseases are now considered to be identical and are termed thrombotic microangiopathies (TMAs) (1). The common pathologies of TMAs are microangiopathic hemolytic anemia (MAHA), debilitating thrombocytopenia, and organ damage caused by microcirculatory disturbances. The principal difference between TTP and HUS is the mechanism of thrombus formation. The pathology of TTP involves thrombus formation attributable to excessive activation of von Willebrand factor (vWF), associated with a decrease in the activity level of ADAMTS13 (a disintegrin; a metalloprotease with 13 thrombospondin type 1 repeats). The pathology of HUS involves thrombus formation, which is attributable to excessive activation of complement components and the development of vascular endothelial cell disorders associated with the complement pathway. Furthermore, in terms of the etiology, HUS can be divided into typical HUS and atypical HUS (aHUS). In aHUS, mutations or autoantibodies lead to dysregulated complement activation, resulting in thrombus formation (2). However, based on recent advances in this field, aHUS was redefined, and secondary TMA was excluded (3, 4). Secondary TMA (or secondary HUS) usually results from a coexisting disease or trigger, such as autoimmunity, transplantation, cancer, infection, certain cytotoxic drugs, or pregnancy.

The underlying mechanisms of secondary TMA are heterogeneous. TMA occasionally accompanies CTDs, such as systemic lupus erythematosus (SLE). However, TMA is only

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a rare complication of polymyositis/dermatomyositis (5). We herein report three cases of dermatomyositis with TMA, one of which was TTP associated with inhibitory autoantibodies against ADAMTS13.

This is a chart review study of the medical records of 159 patients admitted to our hospital between January 1991 and August 2016 for the treatment of polymyositis or dermatomyositis. Among these patients, we found three with TMA.

We reviewed the literature to identify cases of TMA with dermatomyositis. We searched the Medline database using the terms "polymyositis" or "dermatomyositis," combined with "thrombotic microangiopathies," "thrombotic microangiopathy," "thrombotic thrombocytopenic purpura," "atypical hemolytic-uremic syndrome," or "secondary hemolytic-uremic syndrome." The search was performed on papers published from 1946 to June 2016 and was limited to works in the English and Japanese languages. We determined the effectiveness of treatment based on the recovery of the number of platelets.

We evaluated the demographic data, including the age, sex, presence of polymyositis or dermatomyositis, interval from the onset of polymyositis or dermatomyositis to the development of TMA, TMA trigger, and treatment. Our ethics committee approved the study.

Case Reports

Case 1

The patient was a 69-year-old woman. In February 2008, she was diagnosed with dermatomyositis (anti-PL-7-antibody positive) and interstitial pneumonia. Pulsed methylprednisolone (mPSL) (1,000 mg/day for 3 days) was commenced, and prednisolone (PSL) 50 mg/day (1 mg/kg/day) combined with tacrolimus (Tac) 4 mg/day was also administered. She experienced three relapses of the interstitial pneumonia and required sequential increases in the PSL doses. In July 2013 (when she was taking PSL 10 mg/day and Tac 4 mg/day), she was admitted to the hospital because of another relapse of interstitial pneumonia; her serum CK level was 212 U/L but then increased to 615 U/L; the PSL dose was thus increased to 30 mg/day on day 11 of hospitalization. In addition, intermittent intravenous injections of cyclophosphamide (IVCY) (500 mg) were commenced on day 17. However, the serum CK level continued to increase. Therefore, the PSL dose was increased to 80 mg/day on day 28 of hospitalization, and intravenous immunoglobulin (IVIG) was added on day 39.

The serum CK level decreased over time. However, thrombocytopenia was evident on day 28. We initially suspected that the IVCY had induced bone marrow suppression; however, the thrombocytopenia continued. We thought it possible that drug-induced thrombocytopenia was in play and discontinued all oral drugs apart from PSL on day 43 of hospitalization, but the thrombocytopenia continued. The patient began to exhibit abnormal behavior, such as washing her hair with toothpaste. On day 46, the laboratory findings were as follows: Hb level, 12.1 g/dL; white blood cell (WBC) count, 6,760/μL; and platelet count, 35,000/μL. The direct Coomb's test was negative, and the normal coagulation profile rendered disseminated intravascular coagulation (DIC) unlikely. Relevant biochemical findings included a markedly reduced serum haptoglobin level (0 mg/dL) and an elevated level of unconjugated serum bilirubin (1.3 mg/dL). Peripheral blood smears (PBSs) revealed extensive anisocytosis (fragmentation of red blood cells was not evaluated).

These laboratory findings were consistent with TMA. The patient did not have a fever or renal dysfunction. Plasma exchange was initiated on day 46 of hospitalization. After the eighth plasma exchange, the ADAMTS13 activity and anti-ADAMTS13 antibody status were found to be normal and negative, respectively. Therefore, we switched from plasma exchange to daily infusion of fresh-frozen plasma (5 units). The platelet count gradually increased and became normalized on day 115.

Case 2

The patient was a 70-year-old man. In December 2014, he was diagnosed with dermatomyositis (anti-TIF1-γ-antibody positive). Pulsed mPSL (1,000 mg/day for 3 days) was commenced, and PSL (60 mg/day; 1.2 mg/kg/day) combined with IVIG (20 g/day; 400 mg/kg/day for 5 days) was also administered. In February 2015, gastric cancer was identified, and laparoscopic distal gastrectomy was performed. In March 2015, the dermatomyositis relapsed (both skin symptoms and muscle weakness were evident), so the PSL dose was increased to 30 mg/day, combined with IVIG 20 g/day (400 mg/kg/day for 5 days). However, the effects were inadequate. Thus, in April 2015, pulsed mPSL (1,000 mg/day for 3 days) was commenced, and the PSL dose was increased to 70 mg/day (intravenously). Left pleural effusion was noted, and *Mycobacterium tuberculosis* was identified on culture. He was transferred to our hospital for further treatment. On day 8 of hospitalization, sudden thrombocytopenia was evident (platelets 3,000/μL). The other laboratory findings were as follows: Hb level, 7.2 g/dL and WBC count, 4,030/μL. A peripheral blood film revealed fragmented erythrocytes. The direct Coomb's test was negative, and the normal coagulation profile rendered DIC unlikely. The relevant biochemical findings included a markedly reduced serum haptoglobin level (2 mg/dL) and an elevated serum lactate dehydrogenase (LDH) level (442 U/L; reference range, 119-229 U/L). Furthermore, PBSs revealed many fragmented red blood cells. The laboratory data were consistent with TMA. We stopped all drugs except for PSL in order to exclude the possibility of drug-induced thrombocytopenia and commenced plasma exchange. No ADAMTS 13 activity was detectable, and anti-ADAMTS13 IgG autoantibodies were evident. In addition, many von Willebrand multimers were apparent in the blood. We therefore diagnosed him with TTP. We continued daily plasma exchange, but the thrombocytopenia continued. Altered con-

sciousness was evident on day 17 of hospitalization, and convulsions developed on day 18. Therefore, we added rituximab on day 19 and pulsed mPSL (1,000 mg/day for 3 days) and IVIG (17.5 g/day) on day 22. The PSL dose was increased to 70 mg/day. On day 44, the ADAMTS13 activity increased to 14.7%, and the anti-ADAMTS13 autoantibody status was negative. In addition, the haptoglobin level continued to increase. Therefore, plasma exchange was stopped. However, the thrombocytopenia remained (10,000 platelets/μL), and the condition progressed to pancytopenia. Renal dysfunction also emerged (serum creatinine increased from 0.5 to 1.3 mg/dL). The patient was diagnosed with myelodysplastic syndrome (MDS) based on a bone marrow biopsy performed on day 121 of hospitalization. On day 101, bile duct inflammation and septic shock attributable to *Enterobacter cloacae* were apparent. He responded to both antibiotics and endoscopic retrograde cholangiopancreatography (ERCP). However, on day 143, he developed septic shock attributable to multi-drug-resistant *Pseudomonas aeruginosa* (MDRP) and died on day 158.

Case 3

The patient was a 65-year-old woman. In September 1996, she was diagnosed with dermatomyositis (anti-PL-7-antibody-positive) and treated at another hospital. She experienced several relapses. The maximum prior PSL dose was 60 mg/day, and she had received both cyclosporine (CyA) and IVIG. In addition, she was diagnosed with MDS based on a bone marrow biopsy performed in September 2015. In January 2016, the dermatomyositis relapsed once more (serum CK level, 2,402 U/L), and she was admitted to our hospital. The PSL dose was increased to 70 mg/day. On hospital day 17, the platelet count began to decrease. Although all suspect drugs were stopped, the thrombocytopenia continued (39,000 platelets/μL on day 31). TMA was indicated by a decrease in the haptoglobin level to 2 mg/dL and notable erythrocyte fragmentation (1.62%). The other laboratory findings were as follows: Hb level, 10.9 g/dL; and WBC count, 9,970/μL. The direct Coomb's test was negative, the serum LDH level was elevated to 799 U/L (reference range, 119-229 U/L), and the serum creatinine level was elevated from 0.7 to 1.3 mg/dL. No obvious neuropsychiatric symptom was apparent. Based on these findings, plasma exchange was commenced. The ADAMTS13 activity decreased moderately (by 29.1%), and the anti-ADAMTS13 antibody status was slightly positive. We considered that the thrombocytopenia had been associated with secondary TMA rather than TTP. On day 41 of hospitalization, massive bleeding from a duodenal ulcer developed, and platelet transfusion was performed. Subsequently, the platelet count decreased from 34,000/μL to 22,000/μL, suggesting platelet destruction. However, the platelet count then began to increase naturally, and we stopped plasma exchange. On day 65, sudden thrombocytopenia developed once again (the platelet count fell from 97,000/μL to 17,000/μL). We were concerned that a TMA relapse had commenced and restarted plasma exchange. On day 74, she died suddenly from septic shock.

Literature review and assessment of our cases

Clinical features

Our Medline search identified 13 patients with TMA accompanied by polymyositis/dermatomyositis reported between 1946 and June 2016 (6-18). The mean age at the TMA onset was 59.7±9.3 years, and the man-to-woman ratio was 4:12 (25.0% men). The interval from the onset of polymyositis/dermatomyositis to the development of TMA ranged from 1 week to a few years. In our cases, the incidence rate was 1.9% (3 of 159 cases), the mean age at the TMA onset was 70.0±4.1 years, and the man-to-woman ratio was 1:2 (33.3% men). The interval from the disease onset to the TMA development ranged from 6 months to 10 years.

Table 1 lists the clinical features of all 16 patients (including those previously reported and our current patients). We sought to compare the patients with secondary TMA and TTP; however, we were unable to distinguish secondary TMA from TTP because the ADAMTS13 activity had not been measured prior to 2011. The TMA triggers were clear in only three cases. Polymyositis/dermatomyositis was not well controlled in 10 of the 16 cases (62.5%). In terms of clinical symptoms, hemolytic anemia was confirmed in all cases.

Treatments and outcomes

Table 2 lists the treatments and outcomes of all 16 patients. Only 3 of the 16 patients survived (survival rate, 18.8%). Treatment was effective in 6 patients (37.5%); the remaining 10 patients in whom treatment was not effective eventually died. Of the three patients who died despite effective treatment, two died from infections and one from electrocyte imbalance and fluid overload. Of the 10 patients who died without responding to treatment, 4 died of infections, 4 of causes associated with heart problems, 1 of diffuse alveolar hemorrhaging, and 1 of thrombosis.

In terms of treatment, glucocorticoids were given to all 16 patients, and plasma exchange was used to treat 11 (68.8%). One earlier case who survived received vincristine and IVIG, while another received only glucocorticoids. Our surviving cases received glucocorticoids and underwent plasma exchange. Two of our patients responded to such therapy.

Periods from the diagnosis to treatment and from treatment to death

Table 3 lists the intervals from diagnosis to treatment and from treatment to death. The mean time from the development of thrombocytopenia to treatment and from the diagnosis of TMA to treatment was shorter in the treatment-effective group than in the treatment-ineffective group (median, 4.5 days vs. 15.0 days, and 0 days vs. 1.0 days).

All 10 patients in whom treatment was not effective eventually died, and the interval between the TMA onset and death was shorter in the treatment-ineffective group than the treatment-effective group (median, 23.0 days vs. 135.3

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Table 1. Clinical Features of All 16 Patients (previously Reported Patients and Our Patients) with Thrombotic Microangiopathies Accompanied with Polymyositis/ dermatomyositis.

Patients	Age/ Sex	PM or DM	TTP or secondary TMA	From PM/ DM onset to TMA	Trigger	TMA with PM/DM exacerbation	Neurologic manifestation	Hemolytic anemia	Platelet count [/μl]	Renal disfunction	Reference
Treatment-effective group											
1	57/F	PM	N/A	1 week	N/A	(+)	(+)	(+)	16,000	N/A	6
2	42/M	DM	N/A	6 months	N/A	(+)	(+)	(+)	20,000	N/A	7
3	50/F	DM	N/A	16 months	endothelial damage	(-)	(-)	(+)	41,000	(+)	8
4	70/F	PM	secondary TMA	6 years	N/A	N/A	(+)	(+)	32,000	(+)	9
5	69/F	DM	secondary TMA	5 years	N/A	(+)	(+)	(+)	35,000	(-)	Present case (Patient1)
6	75/M	DM	TTP	6 months	N/A	(+)	(+)	(+)	3,000	(+)	Present case (Patient2)
Treatment-ineffective group											
7	65/F	DM	N/A	a few years	N/A	(+)	(+)	(+)	7,000	(+)	10
8	62/F	DM	N/A	a few months	N/A	(-)	(+)	N/A	<100,000	(+)	11
9	73/F	PM	N/A	a few years	Radiation treatment for cervical cancer	(-)	(+)	(+)	26,000	(+)	12
10	59/F	PM	N/A	a few weeks	N/A	(+)	(+)	(+)	16,000	(+)	13
11	60/M	DM	N/A	5 years	N/A	(+)	(+)	(+)	60,000	(+)	14
12	50/F	PM	N/A	8 months	N/A	(-)	(+)	(+)	96,000	(+)	15
13	53/F	PM	N/A	10 days	N/A	(+)	(-)	(+)	63,000	(+)	16
14	48/F	DM	N/A	1 year	pneumoniae, antibiotics	(-)	(+)	(+)	8,000	(+)	17
15	57/M	DM	N/A	13 months	N/A	(+)	(-)	(+)	<100,000	(+)	18
16	65/F	DM	secondary TMA	10 years	N/A	(+)	(-)	(+)	39,000	(+)	Present case (Patient3)

PM: polymyositis, DM: dermatomyositis, TMA: thrombotic microangiopathies, (+) positive, (-) negative, N/A: not available

Table 2. **Treatments and Outcomes of All 16 Patients (previously Reported Patients and Our Patients) with Thrombotic Microangiopathies Accompanied with Polymyositis/dermatomyositis.**

Pt	Age/ Sex	PM/ DM	Treatment									Outcome	Cause of death	Reference
			GC		PE	CAPD	Anti-platelet	VCR	HD	IVIG	RTX	MTX			
Treatment-effective group														
1	57/F	PM	(+)	PSL 100 mg	(+)	(+)	(-)	(-)	(-)	(-)	(-)	(-)	death	electrocyte inbalances and fluid overload	6
2	42/M	DM	(+)	PSL 200 mg	(-)	(-)	(-)	(+)	(-)	(+)	(-)	(+)	alive		7
3	50/F	DM	(+)	N/A	(-)	(-)	(-)	(-)	(-)	(-)	(-)	(-)	alive		8
4	70/F	PM	(+)	PSL 40 mg	(+)	(-)	(-)	(-)	(-)	(-)	(-)	(-)	death	miliary tuberculosis	9
5	69/F	DM	(+)	N/A	(+)	(-)	(-)	(-)	(-)	(-)	(-)	(-)	alive		Present case (Patient1)
6	75/M	DM	(+)	N/A	(+)	(-)	(-)	(-)	(-)	(+)	(+)	(-)	death	cholangitis, sepsis	Present case (Patient2)
Treatment-ineffective group														
7	65/F	DM	(+)	mPSL 2 g q4 h	(+)	(-)	(+)	(-)	(-)	(-)	(-)	(-)	death	pneumonia	10
8	62/F	DM	(+)	N/A	(+)	(-)	(-)	(-)	(-)	(-)	(-)	(-)	death	respiratory fairure	11
9	73/F	PM	(+)	N/A	(+)	(-)	(-)	(-)	(+)	(-)	(-)	(-)	death	heart failure, respiratory failure	12
10	59/F	PM	(+)	N/A	(+)	(-)	(+)	(-)	(+)	(-)	(-)	(+)	death	sepsis	13
11	60/M	DM	(+)	mPSL pulse 1g	(+)	(-)	(+)	(-)	(-)	(+)	(-)	(-)	death	heart failure, pneumonia	14
12	50/F	PM	(+)		(+)	(-)	(-)	(-)	(+)	(-)	(-)	(-)	death	veno-occlusive disease	15
13	53/F	PM	(+)		(-)	(-)	(-)	(-)	(-)	(-)	(-)	(-)	death	acute renal failure	16
14	48/F	DM	(+)	mPSL	(-)	(-)	(-)	(-)	(+)	(+)	(-)	(-)	death	ventricular asystole	17
15	57/M	DM	(+)	mPSL pulse 1g	(-)	(-)	(-)	(-)	(-)	(+)	(-)	(-)	death	diffuse alveolar hemorrhage	18
16	65/F	DM	(+)	N/A	(+)	(-)	(-)	(-)	(+)	(-)	(-)	(-)	death	sepsis	Present case (Patient3)

PM: polymyositis, DM: dermatomyositis, TMA: thrombotic microangiopathies, GC: glucocorticoid, PE: plasma exchange, CAPD: continuous ambulatory peritoneal dialysis, VCR: vincristine, HD: hemodialysis, IVIG: intravenous immunoglobulin, RTX: rituximab, MTX methotrexate, (+) positive, (-) negative, N/A: not available

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Table 3. Period from Diagnosis to Treatment and from Treatment to Death of All 16 Patients (previously Reported Patients and Our Patients) with Thrombotic Microangiopathies Accompanied with Polymyositis/dermatomyositis.

Pt	Outcome	From thrombocytopenia to treatment	From TMA diagnosis to treatment	From TMA onset to death	Reference
Treatment-effective group					
1	death	N/A	N/A	15 days	6
2	alive	0 day	0 day		7
3	alive	N/A	N/A		8
4	death	0 day	0 day	8 months	9
5	alive	18 days	0 day		Present case (Patient1)
6	death	0 day	0 day	151 days	Present case (Patient2)
Treatment-ineffective group					
7	death	N/A	2 days	11 days	10
8	death	45 days	3 days	10 days	11
9	death	0 day	0 day	7 days	12
10	death	N/A	N/A	5 days	13
11	death	5 days	0 day	17 days	14
12	death	N/A	N/A	4 months	15
13	death	N/A	N/A	N/A	16
14	death	N/A	N/A	N/A	17
15	death	11 days	0 day	2 days	18
16	death	14 days	1 day	58 days	Present case (Patient3)

TMA: thrombotic microangiopathies

days).

Discussion

TMA rarely accompanies polymyositis/dermatomyositis; only 13 cases have been previously reported. We treated three additional cases. The underlying mechanisms of TMA are heterogeneous. Matsuyama et al. found severe ADAMTS 13 activity deficiencies in only 16.5% of patients with CTD-TMA, associated with the presence of autoantibodies inhibiting ADAMTS13 (19). The pathogenesis of TTP involves the excessive accumulation (in the circulation) of unusually large vWF multimers because of an extremely low level (<5% normal) of plasma ADAMTS13 vWF-cleaving protease activity; such a deficiency may either be acquired or genetically determined (20). Several factors, including antibiotics, infections, and autoimmune disorders, may trigger the onset of acquired TTP. Few typical cases of TTP have been reported. In some cases, the ADAMTS13 activity decreases in the absence of inhibitory autoantibodies against ADAMTS13, or the ADAMTS13 activity level may in fact be normal. TTP seems to be associated with various pathologies. In our assessment, only 1 (Patient 2) of our 3 patients had TTP, and its trigger was unclear.

The pathogenetic mechanisms underlying the relationship between inflammatory myopathies and TMA remain obscure. Nevertheless, the association between TMA with polymyositis/dermatomyositis is unlikely to be coincidental, given the relative rarity of both conditions. In fact, polymyositis/dermatomyositis was not well controlled in 10 of the 16 cases (62.5%). Under certain circumstances, circulating autoantibodies in patients with autoimmune inflammatory muscle diseases may inhibit the plasma vWF-cleaving protease activity.

According to a review written in the 1960s by Amorosi and Ultmann, only 5% of patients with idiopathic TMA survived (21), with no effective therapy available. However, recent evidence indicates that plasma therapy (alone or in combination with other therapies) dramatically improves the prognosis of patients with TMA. The survival rate of TTP patients has recently been reported to be 96% (22) and was 75% in those with aHUS (23). In the present report, the survival rate of patients with TMA combined with polymyositis/dermatomyositis was 18.8%, which was far lower than the recently reported survival rates of patients with idiopathic TTP or aHUS.

We found no significant difference in the interval from thrombocytopenia to treatment or in that from the diagnosis of TMA to treatment between the treatment-effective and treatment-ineffective groups, indicating that an early diagnosis did not improve the response rate. However, a previous study suggested that the early introduction of plasma exchange for TMA patients might increase the survival rate (24). Therefore, early treatment may be desirable.

The low survival rate of the treatment-effective group (attributable to subsequent complications) is exceptional. The interval between the TMA onset and death was shorter in the treatment-ineffective than in the treatment-effective group. Therefore, the careful management of patients after TMA treatment is essential.

We were unable to identify any association between the TMA symptoms and treatment response. Because controlled prospective studies on TMA patients are lacking, treatment remains largely empirical. Treatment regimens are usually combined and may include glucocorticoids, plasma exchange, and immunosuppressive drugs. We were unable to identify an optimum treatment approach.

Previous reports have only described a single case. To our knowledge, this is the first report to describe multiple cases of polymyositis/dermatomyositis complicated with TMA treated in a single institution. Because polymyositis/dermatomyositis combined with TMA is rare, it is difficult to perform clinical trials. Thus, the gradual accumulation of clinical case reports is important.

Conclusion

We observed three rare cases of polymyositis/dermatomyositis combined with TMA. One case involved typical TTP, and two involved secondary TMA. TMA associated with polymyositis/dermatomyositis is often refractory to treatment and is associated with a poor survival rate. Even if treatment is effective, the mortality rate associated with subsequent complications is high. Therefore, careful attention should be paid to patient management after TMA treatment.

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

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