

[CASE REPORT]

An Autopsy Case of Mixed Connective Tissue Disease Complicated by Thrombotic Thrombocytopenic Purpura

Makiko Yashiro Furuya¹, Hiroshi Watanabe¹, Shuzo Sato¹, Yuya Fujita¹, Jumpei Tenmoku¹, Naoki Matsuoka¹, Tomoyuki Asano¹, Eiji Suzuki², Hiroko Kobayashi¹ and Kiyoshi Migita¹

Abstract:

We herein report a patient with mixed connective tissue disease (MCTD) who had been stable for years but suddenly developed thrombotic thrombocytopenic purpura (TTP). The patient showed a clinical pentad of signs of TTP, low activity of ADAMTS13, and positivity of anti-ADAMTS13 antibodies. She did not respond to plasma exchange or steroid therapy and died five days after admission. An autopsy revealed microthrombi in the brain, heart, kidney, adrenal glands, esophageal submucosa, and bone marrow as well as diffuse alveolar hemorrhaging. Physicians should bear in mind that TTP can occur in MCTD patients regardless of disease activity.

Key words: mixed connective tissue disease (MCTD), thrombotic thrombocytopenic purpura (TTP), a disintegrin-like metalloproteinase with thrombospondin type 1 motif, member 13 (ADAMTS 13), autopsy

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Introduction

Thrombotic thrombocytopenic purpura (TTP) and hemolytic uremic syndrome (HUS) are microvascular occlusive disorders pathologically characterized by thrombotic microangiopathy (TMA), microangiopathic hemolytic anemia, destructive thrombocytopenia, and organ dysfunction caused by platelet thrombi (1). TTP is caused by a deficiency of a disintegrin-like metalloproteinase with thrombospondin type 1 motif, member 13 (ADAMTS13), which specifically cleaves von Willebrand factor (VWF). In the absence of ADAMTS13, unusually large VWF multimers released from endothelial cells are not cleaved appropriately and cause platelet-rich microvascular thrombosis under high shear stress (2, 3).

TTP was first reported by Moschcowitz in 1924 (4), and thrombocytopenia, microangiopathic hemolytic anemia, renal failure, fever, and neurological abnormalities are the classical pentad of signs/symptoms. TTP is classified as congenital TTP, resulting from homozygous or compound heterozy-

gous mutations of the *ADAMTS13* gene, and acquired TTP. Acquired TTP is further classified as acute idiopathic and secondary TTP (5-7). Secondary TTP has been reported to occur in association with malignancy, infection, drugs, pregnancy, bone marrow transplantation, and connective tissue diseases (CTDs) (5, 6, 8). Among CTDs, systemic lupus erythematosus (SLE), antiphospholipid antibody syndrome, adult-onset Still's disease, and systemic sclerosis (SSc) are common causes of TTP (9-17).

Mixed connective tissue disease (MCTD) is a systemic autoimmune disease that has at least two features of three other CTDs [SLE, SSc, and polymyositis (PM)], along with the presence of anti-U1 ribonucleoprotein (RNP) antibodies (18). While a large number of patients with SLE or SSc have been reported (19, 20), MCTD-associated TTP is relatively rare, and only 15 cases have been described to date (21-34).

We herein report a patient with MCTD complicated by TTP and present results of a post-mortem examination as well as a review of the literature and report on an additional 15 patients with this association.

¹Department of Rheumatology, Fukushima Medical University School of Medicine, Japan and ²Division of Rheumatology, Ohta-Nishinouchi Hospital, Japan

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Correspondence to Dr. Hiroshi Watanabe, chiehiro@fmu.ac.jp

Table 1. Laboratory Findings on Admission.

Peripheral blood		Serological tests		Blood gas analysis	
RBC	202×10 ⁴ /μL	CRP	0.81 mg/dL (<0.30)	pH	7.426
Schizocyte	+	ESR	55 mm/h	PCO ₂	30.6 mmHg
Hb	6.3 g/dL	C3	85 mg/dL (86-160)	PaO ₂	148.0 mmHg
Hct	18.0 %	C4	22 mg/dL (17-45)	HCO ₃	19.8 mmol/L
WBC	5,100 /μL	IgG	1,366 mg/dL (900-2,000)	BE	-3.8 mmol/L
Neutrophil	60.0 %	Ferritin	728 ng/mL	Urinalysis	
Monocyte	20.0 %	Anti-nuclear antibody	640 (SP)	pH	5.5
Lymphocyte	15.0 %	Anti U1-RNP antibody	141.0 U/mL	Glucose	Negative
Plt	0.6×10 ⁴ /μL	Anti-Sm antibody	1.9 U/mL	Protein	2+
Blood chemistry		Anti-ds-DNA antibody	0.6 IU/mL	Blood	3+
Total protein	6.2 g/dL	Anti-ssA antibody	137.0 U/mL	Ketones	Negative
AST	43 IU/L (7-33)	Anti-ssB antibody	<0.5 U/mL	Urobilinogen	2+
ALT	18 IU/L (5-30)	aCL	<8 U/mL	Bilirubin	Negative
LDH	1,171 IU/L (119-229)	Anti-β ₂ -GPI	<1.2 U/mL	Leukocyte esterase	Negative
ALP	168 IU/L (80-250)	LAC	1.04 Ratio	Specific gravity	1.015
γ-GTP	10 IU/L (5-55)	MPO-ANCA	<1.0 U/mL		
CK	96 IU/L (60-160)	PR3-ANCA	<1.0 U/mL		
Total bilirubin	5.3 mg/dL	PAIgG	2,370 ng/10 ⁷ cells		
Direct bilirubin	1.1 mg/dL	ADAMTS13 activity	<0.5 %		
BNP	353.5 pg/mL	ADAMTS13 inhibitor	2.5 BU/mL		
BUN	37 mg/dL	Microbiological test			
Creatinine	1.25 mg/dL	CMV-antigenemia	(-)		
Albumin	3.3 g/dL	blood culture	(-)		
Na	133 mEq/L	sputum culture	(-)		
K	3.9 mEq/L	β-D-Glucan	<6.0 pg/mL		
Cl	103 mEq/L				

PAIgG: platelet-associated IgG, ESR: erythrocyte sedimentation rate, aCL: anticardiolipin antibodies, Anti-β₂-GPI: anti-β₂-glycoprotein I antibody, LAC: lupus anticoagulant, ANCA: antineutrophil cytoplasmic antibody, MPO: myeloperoxidase, PR3: proteinase 3, CMV-antigenemia: cytomegalovirus-antigenemia

Case Report

A 59-year-old Japanese woman was admitted to our hospital because of dyspnea and an altered mental status. Three days prior to admission, the patient had felt chest discomfort and general fatigue. On the morning of presentation, she was at home when dyspnea and lethargy developed.

She had noticed Raynaud's phenomenon at 36 years old. Antinuclear antibodies were positive (×1,280, speckled pattern). Anti-U1 RNP antibodies and anti-SSA/Ro antibodies were positive. At 38 years old, she was hospitalized for pneumonia and pleurisy. She received a diagnosis of MCTD based on Raynaud's phenomenon, swollen fingers, polyarthritides, interstitial pneumonia, and positive anti-U1 RNP antibodies. She was also diagnosed with Sjögren's syndrome based on a lip biopsy and sialography. She was initially treated with oral prednisolone (PSL) at a dose of 20 mg/day and showed improvement. The dose of PSL was gradually tapered to 5 mg/day, which was continued for about 20 years.

On admission, she was confused and had a Japan Coma Scale score of 30 points. Her blood pressure was 165/117 mmHg, although later decreased to the normal range. Oxygen saturation was 92% on room air, and oxygen therapy at 4 L/min using a nasal cannula was started. An arterial blood

gas analysis showed a pH of 7.426, a partial pressure of carbon dioxide in arterial (PaO₂) of 148.0 mmHg, and a PaCO₂ of 30.6 mmHg. Her body temperature was 37.1°C. Laboratory data showed hemolytic anemia (hemoglobin 6.3 g/dL, haptoglobin low at 3 mg/dL, and total bilirubin elevated at 5.3 mg/dL) with the presence of red cell fragmentation, thrombocytopenia (platelet count, 0.6×10⁴/μL), and renal dysfunction (blood urea nitrogen 37 mg/dL and creatinine 1.25 mg/dL). Direct and indirect Coombs tests were negative. Anticardiolipin antibodies, anti-b₂-glycoprotein I antibodies, lupus anticoagulant, myeloperoxidase anti-neutrophil cytoplasmic antibody (MPO-ANCA), and proteinase (PR) 3-ANCA were within normal levels. The laboratory findings on admission are shown in Table 1.

A chest X-ray showed cardiomegaly (Fig. 1A). Chest computed tomography (CT) showed pericardial effusion and pleural effusion (Fig. 1B, C). In the emergency room, the patient experienced respiratory arrest and underwent tracheal intubation. A diagnosis of TTP was made, and plasma exchange was immediately carried out. She also received pulsed methylprednisolone (mPSL) (1,000 mg, 3 days) followed by PSL (40 mg/day) and hemodialysis because of oliguria. On day 3, she suffered seizures with no abnormalities on head CT, indicating an association with TTP symptoms. Despite intensive care, she died of multiple organ failure after five days of hospitalization. The clinical course of

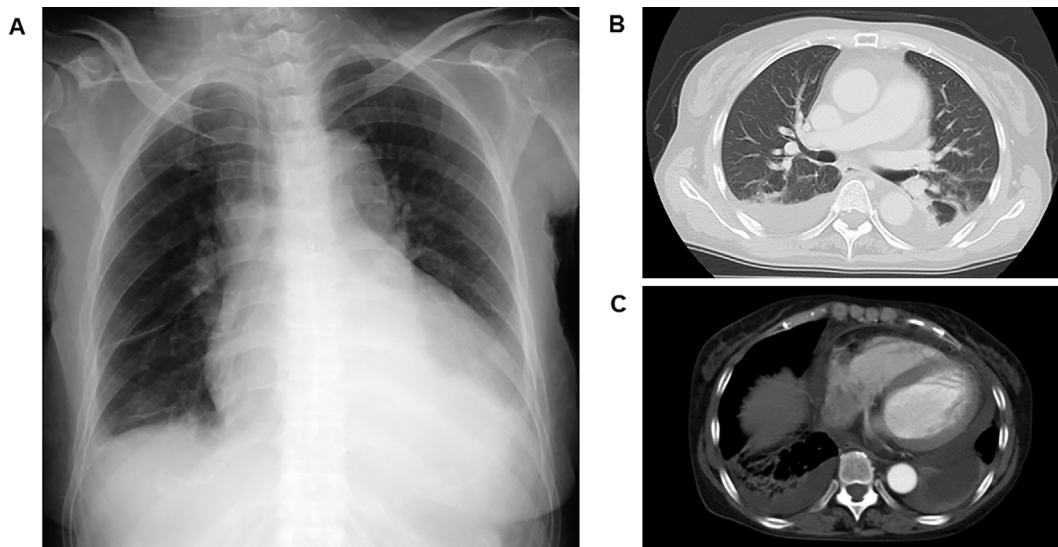


Figure 1. A: Chest radiography on admission showing cardiac enlargement and bilateral pleural effusion. B: Chest computed tomography showing bilateral pleural effusion and bilateral lung fibrosis. C: Chest computed tomography showing pericardial effusion and bilateral pleural effusion.

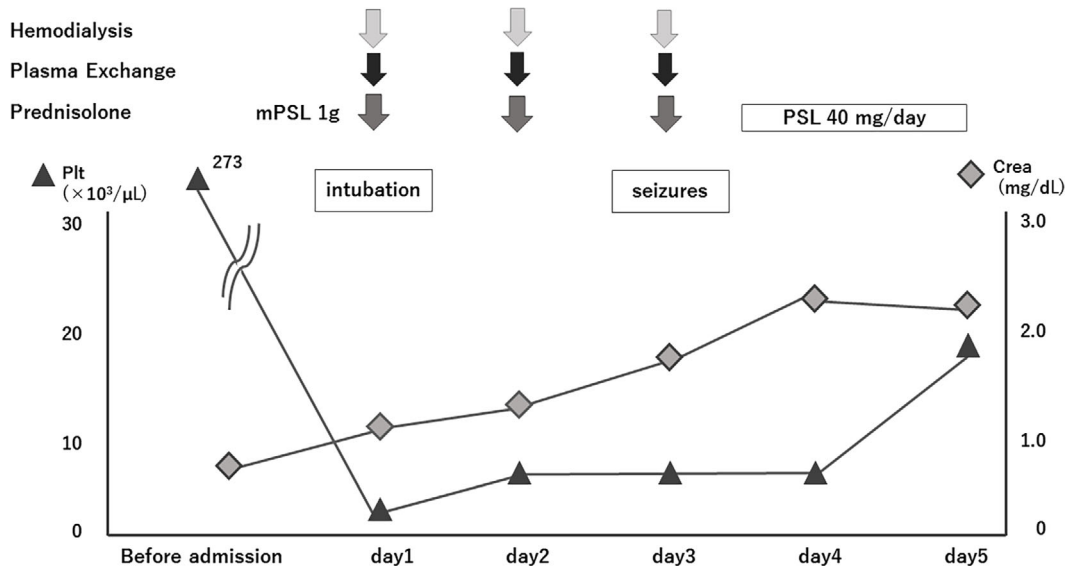


Figure 2. Clinical course of the current case after admission.

this case after admission is shown in Fig. 2.

An autopsy revealed coronary arterial thrombi (Fig. 3A), myocardial hemorrhaging (Fig. 3B), microthrombi and microhemorrhaging of the subcortex and midbrain (Fig. 3C, D), microthrombi in the glomerular capillaries (Fig. 3E), and diffuse alveolar hemorrhaging based on interstitial fibrosis of both lower lung fields (Fig. 3F). Microthrombi were also detected in the afferent arterioles of both kidneys, liver, spleen, adrenal gland, esophageal submucosa, and bone marrow. The ADAMTS13 activity was low at $<0.5\%$, and antibodies to ADAMTS13 were detected. These findings were consistent with a diagnosis of TTP.

Discussion

We reported a patient with MCTD complicated by fatal TTP. The patient showed a clinical pentad of signs of TTP, low activity of ADAMTS13, and positivity of anti-ADAMTS13 antibodies and was thus diagnosed with TTP. She did not respond to plasma exchange or steroid pulse therapy and died five days after admission.

Although the deficiency of ADAMTS13 activity caused by inhibitory autoantibodies plays an important role in patients with acquired TTP (35), how much ADAMTS13 is involved in the pathogenesis of TTP associated with CTD (CTD-TTP) remains unclear. For example, only 40.6% of TTP patients with associated SLE have a severe deficiency

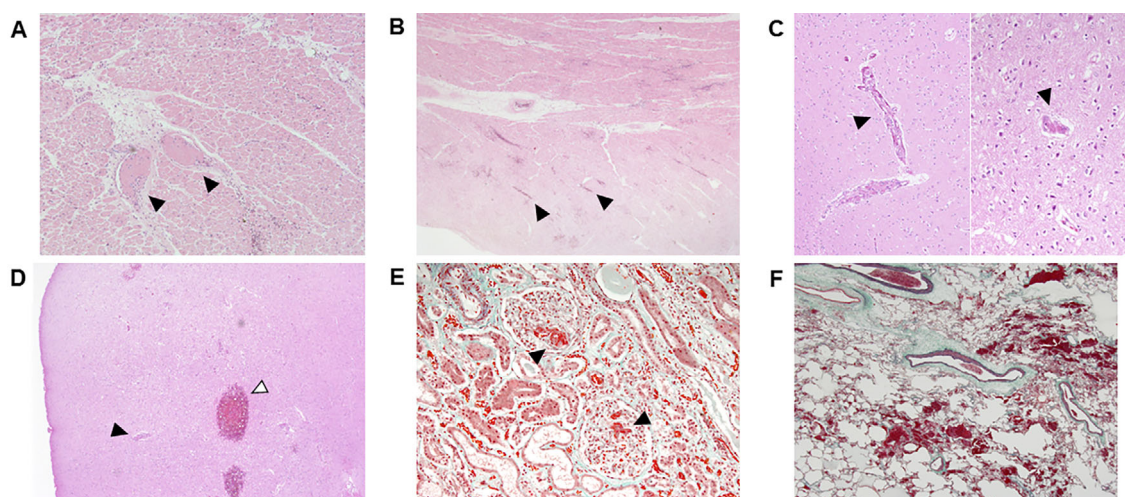


Figure 3. Histological findings of heart (A, B), brain (C, D), kidney (E), and lung (F). A: The black arrowheads indicate coronary arterial thrombi [Hematoxylin and Eosin (H&E) staining, 200×]. B: The black arrowheads indicate myocardial hemorrhaging (H&E staining, 40×). C: The black arrowheads indicate a microthrombus in the subcortex (H&E staining, 100×). D: The black arrowhead indicates a microthrombus, and the white arrowhead indicates microhemorrhaging in the midbrain (H&E staining, 40×). E: The black arrowheads indicate microthrombi in the glomerular capillaries (Elastica-Masson stain, 100×). F: Diffuse alveolar hemorrhaging based on interstitial fibrosis (Elastica-Masson stain, 100×).

Table 2. Characteristics of TTP Associated with MCTD.

Ref.	Age/ Sex	Dominant clinical features of MCTD			Neurological symptoms	Renal involvement	Treatment	Prognosis
		SLE-like	SSc-like	PM-like				
8	29/F	–	+	+	+	–	PSL	Died
9	33/F	+	ND	ND	–	+	PSL, FFP, VIN, AP	Alive
10	60/F	+	–	+	+	+	PE, PSL, IG	Died
11	48/F	ND	ND	ND	+	–	PE, PSL, AP	Alive
12	40/F	+	+	–	+	–	PE, PSL, VIN, AP	Died
13	55/F	ND	ND	ND	+	+	PE, PSL	Alive
14	73/F	+	+	–	+	+	PE, PSL	Died
15	64/M	+	+	–	+	–	PE, PSL	Died
16	15/M	ND	ND	ND	–	–	PE, PSL, VIN, CyA	Alive
17	35/F	ND	ND	ND	+	+	PE, PSL, IG, AP	Alive
18	73/F	–	+	+	+	+	PE, PSL	Died
19	24/F	+	–	+	+	–	PE, PSL	Alive
20	42/F	+	–	+	+	+	PSL, FFP	Alive
21	47/F	+	+	–	–	+	PE, PSL	Died
21	61/F	+	+	–	+	+	PE, PSL	Died
Current case	59/F	+	+	–	+	+	PE, PSL	Died

F: female, M: male, ND: not described, PE: plasma exchange, PSL: prednisolone, FFP: fresh frozen plasma, VIN: vincristine, AP: anti-platelet agents, IG: immunoglobulin, CyA: cyclosporine A

of ADAMTS13 activity (36), although most patients with acquired idiopathic TTP have shown a severe deficiency of ADAMTS13 activity (1-3, 37, 38). Matsuyama et al. found that 16.5% of patients with TMA (TTP and HUS) associated with CTD had a severe deficiency of ADAMTS13 (9). These studies suggest that the pathogenesis of CTD-TTP is complex. Several studies suggest that vasculopathy with endothelial injury and platelet aggregation is intimately in-

involved in the pathogenesis of CTD-TTP, especially in the setting of SLE (39, 40). Furthermore, autoantibodies, such as anti-endothelial cell antibodies, anti-platelet antibodies, and anti-ADAMTS13 antibodies (12, 40, 41), have been reported in patients with CTD-TTP, suggesting that an autoimmune mechanism may be involved in the onset of CTD-TTP.

Thus far, MCTD-TTP has been reported in 16 patients,

Table 3. Clinicopathologic Findings of the Five TTP Patients with Associated MCTD.

Ref.	Age/ Sex	Clinical features of TTP	Pathological findings of TTP associated with MCTD			
			Brain	Kidney	Heart	Other organs
8	29/F	Fulfilled	Thrombi	Thrombi	Thrombi	None
10	60/F	Fulfilled	ND	Glomerular collapse Thrombi in arterioles of the glomerulus	None	Muscle fiber atrophy and inflammatory cell proliferation
14	73/F	Fulfilled	ND	Microthrombi in glomerular capillaries	Thrombi in myocardial vessels	Bladder: thrombi
18	73/F	Fulfilled	None	Fibrin thrombi in arterioles Collapsed capillary loop Mild mesangial proliferation	None	None
Current case	59/F	Fulfilled	Thrombi Hemorrhage	Microthrombi in glomerular capillary	Coronary arterial thrombi Myocardial hemorrhage	Lung: alveolar hemorrhage Liver, spleen, adrenal gland, esophagus, bone marrow: thrombi

The clinical features of TTP include thrombocytopenia, microangiopathic hemolytic anemia, renal failure, fever, and neurological abnormalities.

ND: not described

including the present case (Table 2). Most patients were female (14/16 cases), and the overall mortality was 56.3% (9/16 cases). When accompanied by neurological disorders of TTP, the mortality was worse (80%, 8/10 cases), which is consistent with previous case reports of not only TTP associated with MCTD but also TTP associated with SLE (31, 36). In MCTD-TTP, 10 patients had SLE-like features, 8 had SSc-like features, and 5 had PM-like features. The mortality rate of MCTD-TTP patients having SSc-like features was worse (100%, 8/8 cases) than the overall mortality. Considering that microvascular endothelial cell injury is a critical event in the pathogenesis of SSc, microvascular damage may already exist in MCTD patients who have SSc-like features before developing TTP. In such cases, organ ischemia and functional damage caused by TTP may be more severe, leading to a worse mortality.

In 13 of the 16 MCTD-TTP patients, plasma exchange combined with steroid therapy was performed. However, the mortality rate of those patients was 61.5% (8/13 cases), suggesting that combination therapy of plasma exchange (PE) and a steroid may not be sufficient, although the introduction of PE remarkably improved the prognosis of patients with acquired idiopathic TTP, with an over 80% survival rate (37).

The poor outcome of MCTD-TTP patients treated with PE with steroid therapy also suggests the involvement of complex mechanisms in the disease, and other potential modulators besides ADAMTS 13 may participate in the process of microangiopathy in MCTD-TTP. As described above, previous studies have suggested that an autoimmune mechanism involving autoantibodies may be related to the onset of CTD-TTP. Given that MCTD patients have high levels of anti-endothelial antibodies in their serum, it is possible that endothelial cell abnormalities, including endothelial cell proliferation and endothelial cell injury, may be important factor that cause TTP in MCTD. Recent reports described the widespread use of PE combined with a steroid

and cytotoxic agents (such as cyclophosphamide and mycophenolate mofetil) or rituximab for the treatment of patients with TTP associated with SLE (36). Given that most MCTD-TTP patients have SLE-like features, the use of cytotoxic agents or rituximab in addition to PE combined with steroid therapy may be an option in patients with MCTD-TTP.

Several post-mortem studies of idiopathic TTP have determined that thrombi/emboli followed by hemorrhaging and infarcts in multiple organs (heart, lung, brain, adrenal glands, kidney) are the most common findings (42, 43). However, compared with idiopathic TTP, few studies concerning the pathological features have been reported in secondary TTP, including CTD-TTP. Iwata et al. performed a post-mortem retrospective study of the pathologic features of six patients with secondary TTP, including two patients with dermatomyositis and found no generalized thrombosis in any of the patients, in contrast to the patients with idiopathic TTP. Two of six patients did not show any thrombotic lesions. Furthermore, although all six patients had neurological symptoms, four of them did not show pathological findings in their brain. In CTD-TTP, one of two TTP patients with associated dermatomyositis showed multiple thrombi in the brain, but the other did not show any thrombi or hemorrhaging in the brain (44). These results suggest that vessel occlusion caused by thrombi formation might not occur in the pathogenesis of secondary TTP.

A post-mortem examination of MCTD-TTP was reported in only five patients, including our case (Table 3). Thrombi were found in multiple organs in three patients, including our case. However, thrombi were observed only in the kidney in two patients. A post-mortem examination of the brain was performed in three patients, and two of them showed thrombi in their brain. However, one did not show any pathological findings in the brain, although the patient had neurological features. These results may be consistent with a previous report of Iwata et al. (44).

The present patient had been in a stable condition for over 10 years. It is not clear how often TTP occurs in patients with inactive MCTD, as the disease activity of MCTD has not been well-described in past case reports of MCTD-TTP. However, in patients with SLE-TTP, 35-50% of patients had inactive SLE when they developed TTP (19, 45), and the SLE activity does not correlate with the onset or prognosis of TTP (39), suggesting that the syndrome is different in SLE and should be considered a separate disease entity (40, 46, 47). Given that most MCTD-TTP patients have SLE-like features, it is possible that inactive MCTD patients may also develop fatal TTP. To clarify the pathogenesis of this condition, including whether or not TTP and MCTD are separate clinical entities, more cases will need to be accumulated.

In the present case, we were able to diagnose the patients with TTP on the day of admission and immediately started PE and steroid pulse therapy. Despite early aggressive therapy, the patient did not respond and died five days after being admitted. Given that the patient complained of chest discomfort and general fatigue three days prior to admission, TTP may have occurred in the patient three days before admission and progressed latently, making it too late for the patient to respond to even aggressive therapy.

In conclusion, although TTP is a rare complication of MCTD, the mortality rate is high. Even if MCTD is inactive, the early suspicion and diagnosis of TTP is crucial. To improve its prognosis, aggressive therapy with cytotoxic agents or rituximab in addition to PE and steroids may be needed.

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

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