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CASE REPORT

**Toshiyuki Bohgaki · Atsushi Notoya · Masaya Mukai**
**Michifumi Kohno**

# Thrombotic thrombocytopenic purpura in a patient with rapidly progressive scleroderma

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**Abstract** A 57-year-old man presented with palpitations, shortage of breath on exertion, and rapidly progressive scleroderma. On admission, a computed tomographic scan of his lung showed active interstitial pneumonia. We treated him with D-penicillamine and intravenous pulse methylprednisolone. After this treatment, severe abdominal pain, microangiopathic hemolytic anemia, thrombocytopenia, and progressive renal involvement appeared. We diagnosed him as having systemic sclerosis (SSc) complicated by thrombotic thrombocytopenic purpura. At postmortem, thromboses of capillaries, arterioles, and small arteries were found in several organs. As well as the differential diagnosis of SSc with thrombocytopenia, microangiopathic hemolytic anemia (MAHA), and renal involvement, we diagnosed scleroderma renal crisis (SRC), normotensive renal crisis (NRC), and SSc complicated by TTP. Typical SRC and NRC were excluded because his blood pressure was in the normal range without elevation of plasma renin activity or azotemia over his clinical course. Although distinguishing TTP from renal crisis is difficult, an evaluation of ultra-large multimers of von Willebrand factor (UL-vWF) concentration may be helpful in these situations.

**Key words** Microangiopathic hemolytic anemia · Normotensive renal crisis · Scleroderma renal crisis · Systemic sclerosis · Thrombotic thrombocytopenic purpura

T. Bohgaki[1] (✉) · A. Notoya · M. Mukai · M. Kohno
Division of Clinical Immunology and Hematology, Department of Medicine, Sapporo City General Hospital, N-11, W-13, Chuo-Ku, Sapporo 060-8604, Japan

*Present address*:
[1] Department of Internal Medicine II, Hokkaido University School of Medicine, N-15, W-7, Kita-Ku, Sapporo 060-8638, Japan
Tel. +81-11-716-1161; Fax +81-11-706-7710

## Introduction

Thrombotic thrombocytopenic purpura (TTP) is a rare complication of scleroderma.[1–3] TTP is clinically characterized by microangiopathic hemolytic anemia (MAHA), thrombocytopenia, fever, fluctuating neurological signs, and renal dysfunction. Scleroderma renal crisis (SRC) shares some of these clinical features, including the differential diagnosis of MAHA, thrombocytopenia and renal dysfunction with scleroderma are SRC and TTP. Distinguishing TTP from renal crisis is difficult, due to similarities in their clinical courses. We describe a patient with systemic sclerosis (SSc) complicated by TTP.

## Case report

A 57-year-old man with a 9-year history of rheumatoid arthritis, which was untreated, was admitted to our hospital in August 1997 because of palpitations, short age of breath on exertion, and rapidly progressive scleroderma. He had been well until 5 months earlier, when he began to have edema of the extremities. He was diagnosed as noninsulin-dependent diabetes mellitus (NIDDM) with triopathy and he was on diet therapy. He also had a family history of NIDDM. He was treated with nonsteroidal anti-inflammatory drugs because he had diabetic nephropathy. His chest roentgenogram showed a normal image, and his laboratory data indicated C-reactive protein 1.3 mg/dl. Three months before admission, he experienced palpitations and his fingers, hands, forearms, feet, lower legs, and face became swollen. Raynaud's phenomena also appeared at the same time. The edematous skin rapidly became firm and thickened. In the extremities, the taut skin over fingers and forearms limited full extension, and phalangeal contractures developed.

On examination, he was pale and ankyloglossia. His temperature was 37.1°C, his pulse was 84, and his blood pressure was 128/80 mmHg. His face was swollen and

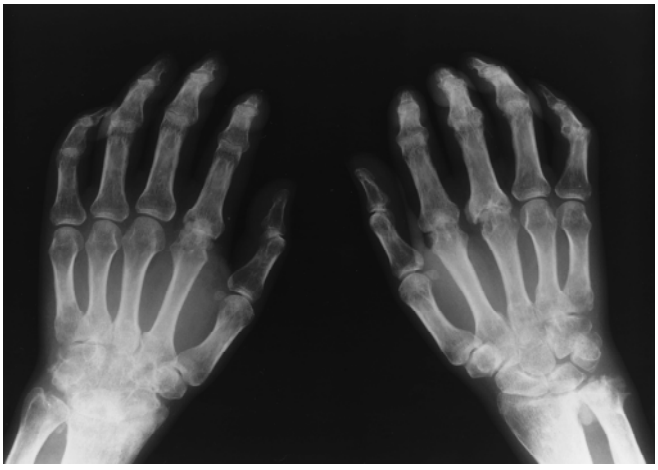

**Fig. 1.** An anteroposterior hands and wrists radiograph showing bony erosion and destruction of the right second and third, and the left second metacarpophalangeal joints and the left carpal bones. In addition, bony resorption of all distal phalanges is seen

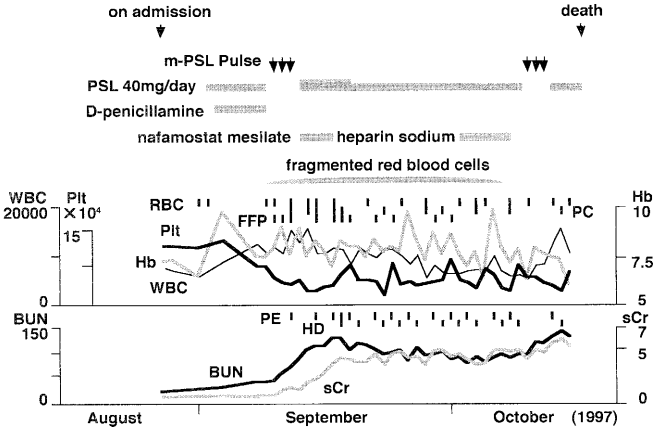


**Fig. 2.** Clinical course after admission. After the treatment with prednisolone, D-penicillamine, and intravenous pulse methylprednisolone, fragmentation of red blood cells was seen on a blood film and renal involvement appeared. *m-PSL Pulse*, intravenous pulse methylprednisolone; *PSL*, prednisolone; *WBC*, white blood cells (/μl); *Plt*, platelets (/μl); *Hb*, hemoglobin (g/dl); *BUN*, blood urine nitrogen (mg/dl); *sCr*, serum creatinie (mg/dl); *RBC*, red blood cell transfusion; *PC*, platelet transfusion; *FFP*, fresh frozen plasma transfusion; *PE*, plasma exchange; *HD*, hemodialysis

looked like a mask. The scleroderma was noted in fingers, forearms, feet, lower legs, and thighs. Digital pitting scars were noted on all fingers, and skin ulcers were noted on the left elbow and the extensor surface of the second proximal interphalangeal joint of the right hand. The posterior cervical region and the dorsal regions of the hands became darkly pigmented and depigmented. The joint pain and swelling were not recognized. Urinalysis was normal. The erythrocyte sedimentation rate was 85 mm/h and C-reactive protein was 1.86 mg/dl. In the peripheral blood, normochromatic anemia with a hemoglobin concentration of 7.3 g/dl without fragmentation and thrombocytopenia with a platelet count of $11.6 \times 10^4$/μl were noted. Fasting plasma glucose was 98 mg/dl and hemoglobin alc was 6.8% on diet therapy. Blood urea nitrogen (BUN), serum creatinine (sCr), and electrolytes were normal, but lactate dehydrogenase (LDH) (1057 IU/l (180–410 IU/l)) was elevated. Coagulation tests were in the normal range. Coombs' test was negative. Antinuclear antibody (ANA) (1:2560; homogeneous pattern), rheumatoid factor (44 IU/ml), and anti-Scl 70 antibody were positive. Lupus anticoagulant (LA), anticardiolipin antibody, cytoplasmic antineutrophil cytoplasmic antibody (ANCA), and myeloperoxidase-ANCA (MPO-ANCA) were negative. A computed tomographic scan showed mild fibrotic changes in both lower lung fields. His pulmonary artery pressure with 2D-echocardiography was 40 mmHg.

We diagnosed him as having systemic sclerosis (SSc) (Fig. 1) with mild pulmonary hypertension and active interstitial pneumonia. Prednisolone and D-penicillamine were started, and intravenous pulse methylprednisolone was added (Fig. 2). After this treatment, severe abdominal pain developed and a blood film showed the fragmentation of blood cells. Further investigations revealed total bilirubin 2.0 mg/dl, LDH 1805 IU/l, haptoglobin 11.8 mg/dl, BUN 43 mg/dl, sCr 0.8 mg/dl, plasma renin activity (PRA) 3.4 ng/ml, angiotensin-II (AT-II) 23 pg/ml, and fibrinogen degradation products 14.6 μg/ml. A diagnosis of TTP was made on the basis of rapidly progressive renal involvement, MAHA, and thrombocytopenia. Although the patient became drowsy and spoke strangely after this, clear conscious later returned. However, in spite of treatment with prednisolone, fresh frozen plasma, and plasma exchange, melena appeared and he died of respiratory failure with interstitial pneumonia.

At autopsy, the histopathological skin findings were consistent with scleroderma. In the lungs, interstitial pneumonia and loose fibrous intimal thickening with narrowing of the lumen were shown. In the kidneys, the histopathological findings in the interlobular artery, arterioles, and capillary loops showed the fragmentation of blood cells and focal fibrinoid necrosis. The most striking findings were multiple fibrin and hyaline thrombi of small vessels and arterioles in the lungs, heart, and kidneys, and histopathological features typical of TTP (Fig. 3). Most of the glomeruli showed diffuse and nodular diabetic glomerulosclerosis. There was no postmortem examination of the brain.

## Discussion

TTP is clinically characterized by MAHA, thrombocytopenia, fever, fluctuating neurological signs, and renal dysfunction. In addition, patients with TTP show hematuria, nausea, abdominal pain, and joint pains, and are seropositive for ANA about 20%.[4] Thrombi and fibrin depositions are recognized in microscopic findings. In this case, the patient was treated with prednisolone and D-penicillamine because of rapidly progressive scleroderma complicated by interstitial pneumonia. During these therapies, severe abdominal pain, MAHA, thrombocytopenia, and renal insuf-

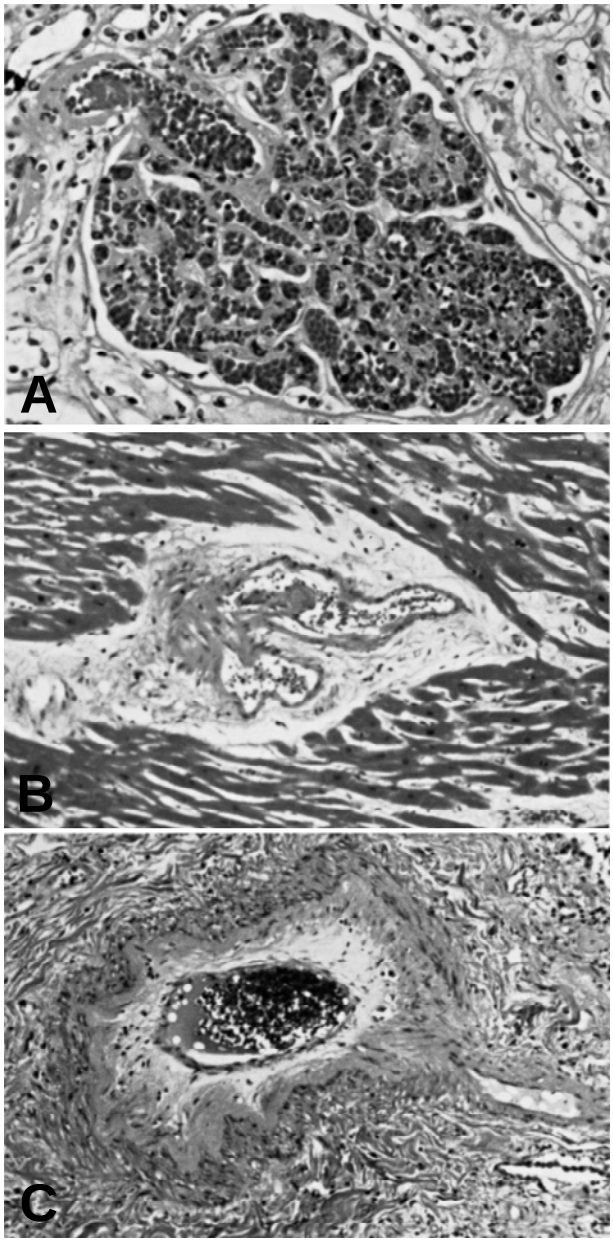


**Fig. 3.** **A** Thrombi, fragmentation of blood cells, and nodular diabetic glomerulosclerosis in the capillary loop. There are no findings of necrotizing glomerulonephritis or crescent formations. **B** Microthrombi in the lumens of small intramyocardial branches of the coronary arteries. **C** Microthrombi and loose fibrous intimal thickening with narrowing of the lumen in the lungs. ×200

ficiency appeared. We diagnosed him as having SSc complicated by TTP. Although he was treated with prednisolone, fresh frozen plasma, and plasma exchange, his symptoms deteriorated and he died of respiratory failure. In this case, the differential diagnosis of SSc with thrombocytopenia, MAHA, and renal involvement included SRC and SSc complicated by TTP. SRC is clinically characterized by hypertension, retinopathy, elevating PRA, and rapid renal failure.[5] Patients with rapidly progressive diffuse scleroderma early in their disease course are at greatest risk of SRC.[6] According to Helfrich et al.,[7] in 11% of patients with renal crisis, the blood pressure remains within the normal range. The diagnosis of normotensive renal crisis (NRC) depends on the presence of MAHA, elevated PRA, and azotemia. Histopathologically, glomerulosclerosis and fibrous endothelium of arterioles are seen in both NRC and SRC. The formation of thrombi, necrosis of arterioles, and collapse of the glomeruli are shown only in NRC.

In a report of six of 100 SSc patients who were seropositive for MPO-ANCA, Endo et al.[8] described rapidly progressive renal failure without signs of malignant hypertension in all six cases, and normal ranges of blood pressure, PRA, and AT-II in five. They observed anemia, thrombocytopenia, multiple autoantibodies, fever, and pulmonary hemorrhage in these cases, but did not find MAHA or headache. The histopathological findings looked like MPO-ANCA-associated glomeruronephritis. In addition, Quereda et al.[9] described the possible relationship between LA and the development of thrombosis in the small renal vessels as being a trigger for SRC.

Typical SRC was excluded because in our case the blood pressure was within the normal range throughout the clinical course. In addition, MPO-ANCA and LA were negative, and necrotizing glomerulonephritis and crescent formations were not found. Although our case was afebrile with no purpura, MAHA, thrombocytopenia, and fluctuating neurological signs were seen. Helfrich et al.[7] distinguished TTP from NRC by the paucity of purpura and the presence of fever and neurological signs. In this case, there were systemic thrombi formations, fragmentation of blood cells, and no signs of vasculitis.

Some authors[10–12] have reported TTP during D-penicillamine therapy, and these cases led to remission when treated with prednisolone, fresh frozen plasma, and plasma exchange after discontinuation of the D-penicillamine therapy. Although the mechanisms of drug-induced TTP are not clear, the reactive sulfhydryl group on penicillamine could bind with membrane proteins and alter them sufficiently to induce antibody formation either to the drug acting as a hapten or to unmasked antigenic determinations on the membrane. Recently, Furlan et al.[13] and Tsai and Lian[14] suggested that loss or dysfunction of von Willebrand factor-cleaving protease because of inhibitors, which were shown to be immunoglobulin G antibodies, resulted in increases in ultra-large multimers of von Willebrand factor (UL-vWF) in patients with acute TTP. UL-vWF, which is secreted from endothelial cells, may be more likely to bind platelets and induce systemic thrombi formations. Although distinguishing TTP from renal crisis is difficult, as in our case, an evaluation of UL-vWF concentration may be helpful in these situations.

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