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CASE REPORT

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Normotensive scleroderma renal crisis with diffuse alveolar damage after corticosteroid therapy

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Abstract A 68-year-old woman with systemic sclerosis developed acute respiratory failure due to diffuse alveolar hemorrhage and normotensive scleroderma renal crisis (SRC) shortly after the initiation of corticosteroid therapy. Treatment with angiotensin-converting enzyme inhibitor and plasmapheresis had failed in this patient. Autopsy showed diffuse alveolar damage and thrombotic microangiopathy. The sequence of events in this patient clarifies the pathologic process of normotensive SRC, and suggests a causative role of corticosteroid therapy and normotensive SRC.

Key words Corticosteroid · Diffuse alveolar damage (DAH) · Scleroderma renal crisis (SRC) · Systemic sclerosis (SSc) · Thrombotic microangiopathy (TMA)

Introduction

Scleroderma renal crisis (SRC) is well known as one of the life-threatening complications of systemic sclerosis (SSc).[1–3] Precipitation of SRC by high-dose corticosteroid use, especially in normotensive patients with thrombotic microangiopathy (TMA), is well described.[2,3] Normotensive SRC has a grave prognosis and often presented with severe lung disease, such as diffuse alveolar hemorrhage (DAH).[2] However, the pathologic mechanisms remain unknown. Here we report a case of SSc, in which normotensive SRC with DAH developed shortly after the initiation of corticosteroid therapy.

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Case report

A 68-year-old woman was admitted to our hospital in October 2003 suffering from dyspnea and low-grade fever. She had been well until January 2003, when she noticed Raynaud's phenomenon. She visited another hospital because of exertional dyspnea 4 months earlier, in July 2003, where she was diagnosed as having SSc with interstitial pneumonia according to the results of forearm skin biopsy and computed tomography of the chest. She also noticed a low-grade fever and had difficulty swallowing solid foods at that time. She had never had prior corticosteroid or immunosuppressive therapy.

On admission, temperature was 37.3°C, pulse 88 and regular, respiration 28, and blood pressure 104/80 mmHg. Skin thickening with edematous change in the face, extremities, and anterior chest was compatible with cutaneous involvement of early diffuse-type SSc. Heart sounds were normal, but bibasilar fine crackles were heard. Laboratory data on admission were as follows: WBC 7500/μl, hemoglobin 11.7 g/dl, platelet count 171 × 10^3/μl, fibrinogen 362 mg/dl, FDP 8.6 μg/ml, D-dimer 6.6 μg/ml, blood urea nitrogen 9 mg/dl, creatinine 0.4 mg/dl, lactate dehydrogenase 452 U/l, normal transaminases, C-reactive protein 5.45 mg/dl, IgG 2380 mg/dl, IgA 443 mg/dl, IgM 175 mg/dl, haptoglobin 62 mg/dl, CH_{50} 36.4 U/ml, antinuclear antibodies ×5120 with speckled pattern, and anti-Scl-70 strongly positive. The tests for anti-DNA, antiribonucleoprotein, antineutrophil cytoplasmic antibodies (ANCA) by immunofluorescence assay, myeloperoxidase-ANCA, proteinase 3-ANCA by enzyme-linked immunosorbent assay, antiglomerular basement membrane antibodies, and direct/indirect Coombs tests were all negative. Anti-cytomegalovirus (CMV)-IgG was strongly positive, but anti-CMV-IgM was negative. Soluble thrombomodulin was elevated, at 29.3 U/ml (normal range 10.4–23.4), which indicated vascular endothelial damage. The urinalysis was unremarkable. Chest radiograph and computed tomography (Fig. 1A,B) showed a pericardial effusion and interstitial pneumonia. For the treatment of pericarditis, intravenous administration of methylpredni-

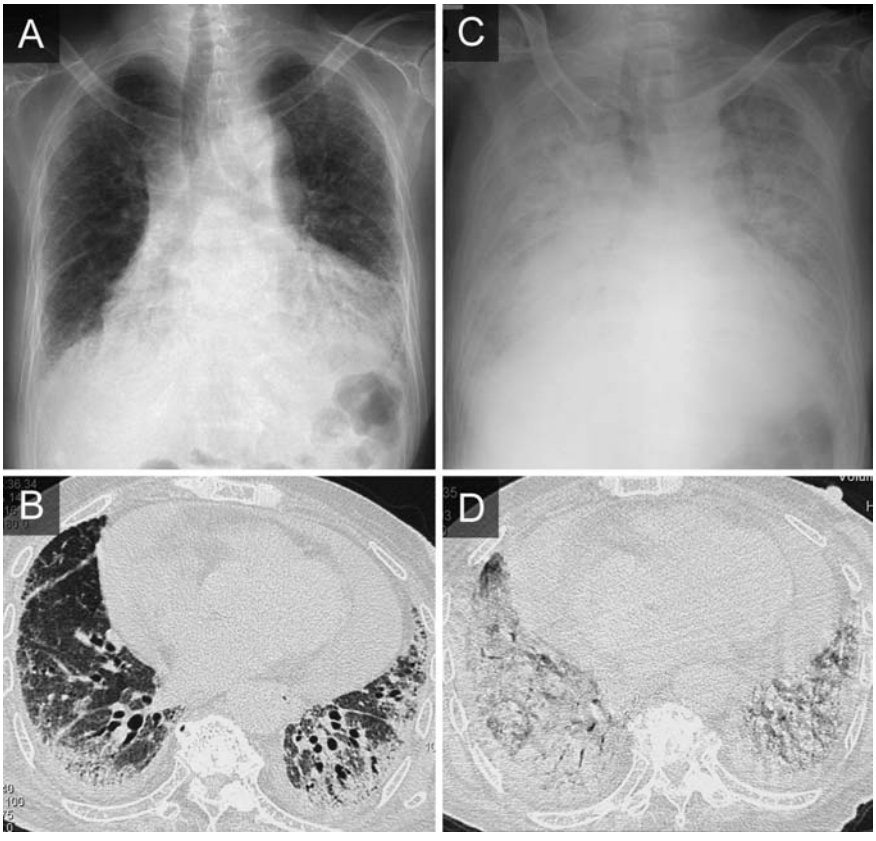

Fig. 1. Chest radiograph and computed tomography obtained on admission (**A,B**) and on the 12th hospital day (**C,D**). **A** Enlargement of the cardiac shadow and diffuse peripheral reticulonodular infiltrates in the lungs. **B** Moderate pericardial effusion and interstitial infiltrates, mostly ground-glass opacities and scant honeycombing, with traction bronchiectasis, which suggested an active stage of interstitial pneumonia. Pericardial effusion and interstitial lung shadows on admission had apparently worsened compared with June 2003. **C,D** Diffuse consolidation in both lungs, which was due to diffuse alveolar hemorrhage confirmed by bronchoalveolar lavage analysis. There was almost no change in the amount of pericardial effusion (**B,D**)

solone at 40 mg/day was started on the third hospital day. Dyspnea was temporarily improved. On the 12th hospital day, the patient suddenly developed acute respiratory failure with diffuse pulmonary consolidation (Fig. 1C,D), which required mechanical ventilation. Antimicrobial agents, including gancyclovir and intravenous sulfamethoxazole trimethoprim, and gabexate mesilate were empirically administered. The dose of corticosteroid was empirically increased to suppress excess lung inflammation and to control the suspected underlying pulmonary capillaritis. The decreased haptoglobin and the presence of fragmented red cells (3.9%) and severe thrombocytopenia led us to the diagnosis of TMA. Plasma renin activity was increased, 18 ng/ml per hour (normal range 0.3–2.9). Soluble thrombomodulin was further elevated (57.0 U/ml). Analysis of bronchoalveolar lavage fluid showed that she had DAH. Serum β-D-glucan was normal, but CMV pp65 leukocytic antigenemia, as determined using monoclonal antibody HRP-C7,[4] was positive (5/30 000 cells) on the 14th hospital day, which made us hesitate to employ additional cyclophosphamide therapy. Serum creatinine began to rise from the 13th hospital day. The clinical course strongly suggested that she had normotensive SRC (Fig. 2). Treatment with angiotensin-converting enzyme inhibitor and plasma exchange was instituted. However, her renal function progressively deteriorated, and hemodialysis was required on the 16th hospital day. Blood pressure never became hypertensive over the entire clinical course. Moreover, vasopressors had been required to maintain her blood pressure after she suffered alveolar hemorrhage. Negative results of repeated blood cultures and plasma endotoxin measurements denied she had septic shock. In spite of the intensive treatment, the patient died from multiple organ failure on the 21st hospital day. Autopsy showed diffuse alveolar damage (DAD) with DAH superimposed on chronic interstitial pneumonia with fibrotic nonspecific interstitial pneumonia pattern in the lungs, thrombi in microvasculature of the kidneys consistent with the features of TMA, acute pancreatic necrosis, and multiple mucosal erosions of the digestive tract (Figs. 3 and 4). Capillaritis and microvascular thrombi in the lung specimens were not observed. There was no significant evidence of bacterial infections. In situ hybridization using CMV-specific DNA probe showed no evidence of intracellular CMV infection in the lung and kidney specimens.

Discussion

Normotensive SRC has been reported to be frequently associated with TMA, thrombocytopenia, DAH, and precipitation by high-dose corticosteroid treatment.[2] The rapid sequence of events in this patient, starting with corticosteroid use followed by the asymptomatic decrease of haptoglobin and platelet count, which may be the early signs of

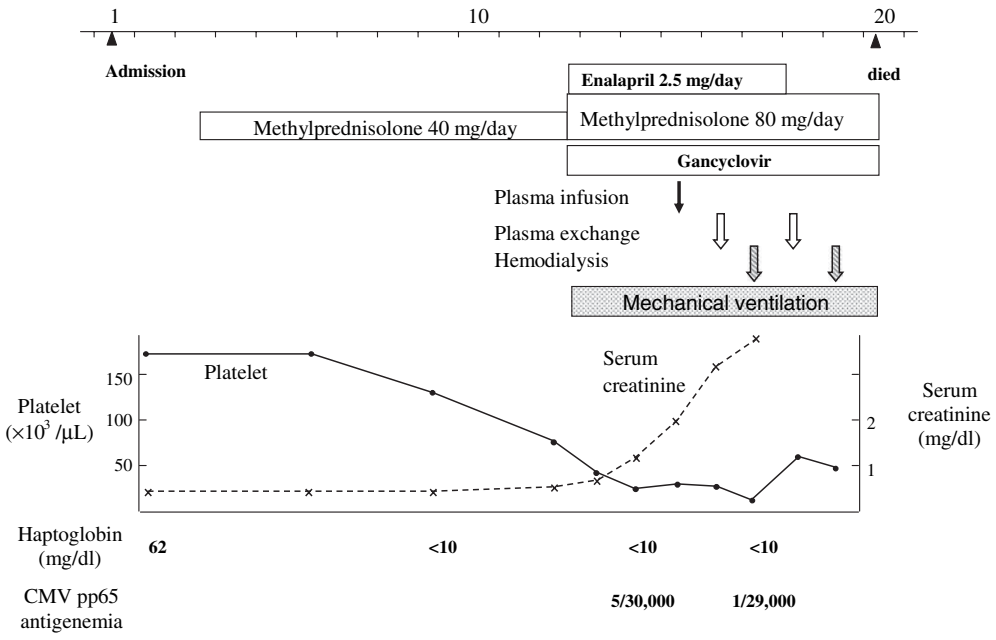

Fig. 2. Clinical course after admission

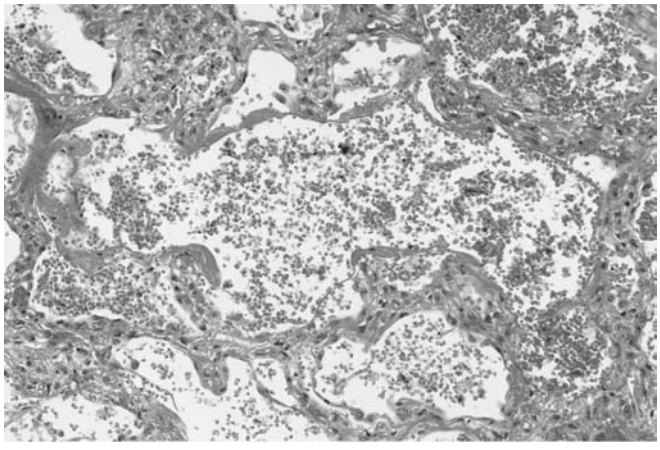

Fig. 3. Lung necropsy specimen from right upper lobe shows hyaline membrane formations and accumulations of red blood cells in alveolar spaces, and relatively uniform interstitial thickening and cellular infiltration (H&E, ×100)

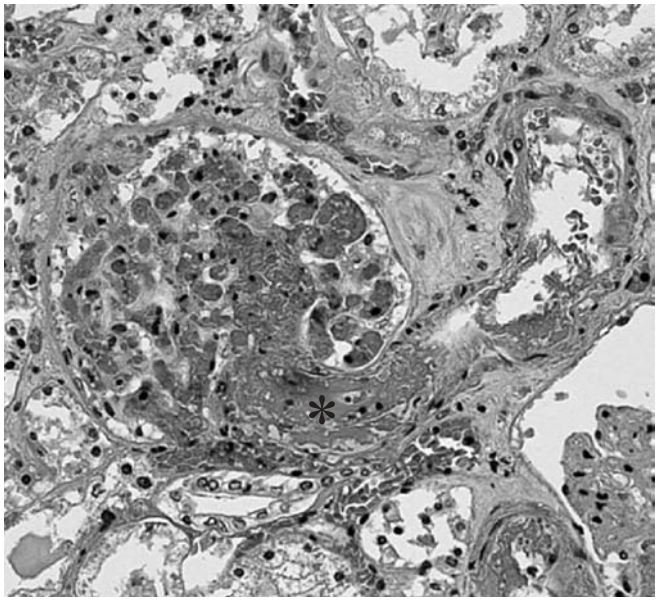

Fig. 4. Renal necropsy specimen shows microthrombi in the afferent/efferent arterioles (*asterisk*) and glomerular vasculature (H&E, ×200)

TMA, then the development of acute respiratory and renal failure due to DAD and renal microvascular emboli strongly suggests that TMA triggered and/or accelerated by the corticosteroid therapy caused DAD and normotensive SRC.

Diffuse alveolar hemorrhage has many clinical etiologies as well as variety of underlying histologic patterns.[5] Bar et al. coined the term "scleroderma pulmonary renal syndrome (SPRS)" for the patients with SSc who presented with DAH and acute renal failure and presented pulmonary capillaritis as the underlying histological pattern of DAH in SPRS.[6] However, SPRS includes ANCA-related vasculitis accompanying SSc; there are SPRS patients, like this case, without ANCA and antiglomerular basement membrane antibodies. Those patients were reported to be frequently associated with microangiopathic hemolytic anemia, which can be included in TMA.[2,6] Diffuse alveolar hemorrhage can also occur secondary to DAD, which refers to a response of the lung to an acute injury from variety of sources including TMA, as a result of widespread injury to the epithelial lining and alveolar-capillary basement membranes.[5,7] Although pulmonary microvascular emboli, a characteristic pathological feature of TMA, were not observed in the autopsied lung specimens, the patient's

clinical course strongly suggests DAD was caused by TMA in this case.

It has been postulated from in vitro studies and several clinical observations[8–10] that corticosteroids have procoagulant effects, but detailed mechanisms of procoagulant actions of corticosteroid and the role of corticosteroid in the pathogenesis of SRC have remained unknown. A recent study indicated that corticosteroid could markedly potentiate tissue factor-dependent procoagulant activity to thrombin by increasing the availability of membrane proteolytically activatable thrombin receptor (PAR-1) in human vascular smooth muscle cells.[11] Endothelial injury is present in all involved organs in scleroderma.[12] Increased levels of soluble thrombomodulin before corticosteroid treatment in this patient also indicated vascular endothelial damage. It might be a reasonable explanation for development of TMA in SSc after corticosteroid use that corticosteroid induces a hypercoagulable state by upregulation of PAR-1 expression from vascular smooth muscle cells, which may be substantially exposed to the blood flow by continuous endothelial cell damage presented in SSc, and lead to TMA.

Another intriguing finding in this patient was that reactivated CMV infection, indicated by the presence of anti-CMV-IgG antibodies and CMV pp65 antigenemia at the onset of normotensive SRC, was observed at the onset of acute respiratory failure.[13,14] It has been suggested that CMV infection may have a role in the pathogenesis of SSc.[15,16] Moreover, a possible association between CMV infection and TMA has been reported, especially in patients who received organ transplants or with human immunodeficiency virus (HIV) infection.[17,18] A negative result of cytomegalovirus infection determined by in situ hybridization study of autopsied specimens might be due to intensive gancyclovir therapy. Together with the relevant literature, we speculate that CMV reactivation possibly induced by high-dose corticosteroid use may have some contributory effects to the onset of TMA in this patient. Further studies are needed to define the role of CMV reactivation in the pathogenesis of normotensive SRC.

Normotensive SRC associated with DAH or TMA-related SPRS has a grave prognosis.[2,6] Therapeutic roles of angiotensin-converting enzyme inhibitors, plasmapheresis, and immunosuppressive treatment in normotensive SRC are uncertain, and they did not work in this patient. High-dose corticosteroids have often been successfully used for the treatment of pulmonary-renal syndrome associated with other autoimmune diseases, such as systemic vasculitides, systemic lupus erythematosus, and Goodpasture's syndrome.[19] Although this therapeutic regimen appears to be beneficial in myeloperoxidase-ANCA-related SPRS,[20–22] this might not be a beneficial regimen in the treatment of TMA-related SPRS in view of a possible causative role of corticosteroids in normotensive SRC. There are suggestions that cyclophosphamide may be beneficial for the treatment of interstitial pneumonia associated with SSc,[23] but the efficacy of this drug for the treatment of TMA-related SPRS is uncertain.

Other treatment strategies supported by the evidence concerning the pathogenesis of TMA-related SPRS should be explored. This case report may provide some insight into the mechanism of DAH and normotensive SRC development after high-dose corticosteroid treatment. Further studies are needed to clarify the disease entities of SPRS and to elucidate the pathogenesis of this disorder.

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