CASE REPORT

Glucocorticoid-induced Normotensive Scleroderma Renal Crisis: A Report on Two Cases and a Review of the Literature in Japan

Akihito Maruyama, Takao Nagashima, Kohei Ikenoya, Yoko Aoki, Yasushi Matsuyama, Masahiro Iwamoto and Seiji Minota

Abstract

We herein report the findings of 2 cases of normotensive scleroderma renal crisis (SRC) that developed soon after the commencement of a glucocorticoid therapy. We also review 8 cases of normotensive SRC reported in Japan, including our cases. The common characteristics of these 8 cases are as follows: the recent onset of systemic sclerosis, the presence of diffuse skin sclerosis, the presence of myositis and/or serositis, a high titer of antinuclear antibody and positivity for anti-Scl-70 antibody. In 7 of the 8 patients, thrombotic microangiopathy developed within one month of starting the glucocorticoid treatment. We should be careful with the use of glucocorticoids in systemic sclerosis patients exhibiting these features in order to avoid cases of normotensive SRC.

Key words: glucocorticoid, normotensive renal crisis, systemic sclerosis, thrombotic microangiopathy, thrombotic thrombocytopenic purpura

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Introduction

Scleroderma renal crisis (SRC) is characterized by severe hypertension and progressive renal failure, and is one of the life-threatening complications of systemic sclerosis (SSc) (1). SRC is an infrequent complication of SSc in Japan, with a reported incidence of 1.5-5.1% (2-4). The risk factors for SRC include diffuse skin involvement, the rapid progression of skin thickening, a disease duration <4 years, positivity for anti-RNA polymerase III antibody, anemia, cardiac events (pericardial effusion and congestive heart failure) and high-dose glucocorticoid (GC) therapy (1). Although severe hypertension is usually regarded as one of the features of SRC, patients with a normal blood pressure (BP) have also been reported as a subset of this condition (5). We herein present two cases of normotensive SRC developing soon after the commencement of GC therapy. In both patients, thrombocytopenia was an early manifestation of thrombotic microangiopathy (TMA) that occurred within 3 weeks of starting GC therapy. The TMA can be interpreted as being GC-induced in these cases. We also reviewed 6 other cases of normotensive SRC reported in Japan in order to elucidate the characteristics of this rare condition in Japanese patients.

Case Reports

Case 1

A 66-year-old man, diagnosed as having diffuse scleroderma 1.5 years earlier, was admitted to our hospital for an evaluation of dyspnea. His BP was 120/80 mmHg, and his modified Rodnan total skin thickness score (mRTSS) was 29. He did not present with myalgia. An examination of the complete blood count revealed a leukocyte count of 4 600/μL, a hemoglobin level of 11.7 g/dL and a platelet count of 23.4×10⁴/μL. His urinalysis was normal, his serum creatinine was 0.86 mg/dL, his serum creatine kinase (CK) was 488 U/L (normal: <150) and his C-reactive pro-
tein (CRP) was 4.4 mg/dL. The antinuclear antibody (ANA) was positive at 1:5,120 (with nucleolar and homogeneous patterns) and the anti-Scl-70 antibody was positive at 1:64. The anti-RNA-polymerase III antibody was negative. Computed tomography (CT) of the chest showed a pleural effusion on the left, a small pericardial effusion and interstitial lung disease (ILD). The pleural fluid sample obtained using thoracocentesis was an exudate with a predominance of lymphocytes (940 cells/μL with 78% lymphocytes). Treatment with prednisolone (PSL) was started at 20 mg/day (0.4 mg/kg) for pleuritis and subclinical myositis, with the dose being increased to 30 mg/day after 10 days. After 18 days of PSL treatment, he suffered from a sudden loss of consciousness due to a complete atrioventricular block. As a result, a permanent pacemaker was immediately implanted.

On the same day, a slight decrease in the platelet count was noted (17.7×10^3/μL), and the count decreased further to 6.5×10^3/μL after two weeks. The serum haptoglobin level was undetectable, the direct Coombs test was negative and erythrocyte fragmentation was not seen on a blood smear, while his hemoglobin, serum creatinine and lactate dehydrogenase (LD) remained unchanged. Over the next 2 weeks, however, his hemoglobin level decreased to 10.2 g/dL; and his serum creatinine rose to 0.97 mg/dL. His plasma renin activity increased slightly to 3.6 ng/mL/hr (normal: 0.3-2.9). The level of a disintegrin-like and metalloproteinase with thrombospondin type 1 motif 13 (ADAMTS13) activity was 29.1%. She had edema of the legs, and a tendon friction rub was detected at the right ankle joint. Her leukocyte count was 7 400/μL, her hemoglobin level was 10.8 g/dL, and her platelet count was 36.1×10^4/μL. Her urinalysis was normal, serum creatinine was 0.55 mg/dL, LD was 629 U/L, serum CK was 860 U/L, CRP was 2.89 mg/dL, and KL-6 was 5 130 U/mL (normal: <500). The ANA was positive (1: 20,480) with nucleolar and homogeneous patterns, the anti-Scl-70 antibody was positive (1:256), the rheumatoid factor was positive (1:80) and the anti-cyclic citrullinated peptide antibody was positive (17.5 U/mL, normal: <4.5). The anti-RNA-polymerase III antibody and MPO-ANCA were negative. Echocardiography revealed a massive pericardial effusion with a normal cardiac contraction. A radiograph of the hand showed ankylosis of the carpal bones and the subluxation of the metacarpophalangeal joints with erosions. Chest CT showed ILD and a large amount of pericardial effusion without any pleural effusion. The diagnosis was SSc with periarteritis and myositis overlapping with RA. The PSL therapy was increased to 30 mg/day (0.6 mg/kg) to treat her myositis, periarteritis and fever. After 16 days, thrombocytopenia was detected (14.9×10^3/μL). Her serum creatinine increased slightly to 0.75 mg/dL and her serum LD increased to 836 U/L. A urinalysis showed protein 1+ and occult blood 2+, but there were less than 10 red blood cells per field. Her haptoglobin level was undetectable, the direct Coombs test was negative and the plasma renin concentration was 48 pg/mL (normal: 2.5-21). Erythrocyte fragmentation was not seen. The ADAMTS13 activity was 29.1%. She was diagnosed with TMA, and treatment with plasma exchange and captopril was started. Her platelet count, LD and serum haptoglobin gradually returned to normal, but her serum creatinine increased further to 1.41 mg/dL after one month. Although her BP rose as high as 164/96 mmHg following the deterioration of her renal function, her average BP remained in the normal range throughout the captopril treatment course. A renal biopsy was performed one month later and the specimen showed ischemic and microangiopathic changes (Figure). She was discharged 4 months after admission with a serum creatinine level of 4.84 mg/dL. Hemodialysis was commenced at 9 months after discharge. She was soon admitted to another hospital with fever, arthritis, dyspnea and large pericardial and pleural effusions. She died 14 months after discharge despite being treated with high-dose PSL.

**Discussion**

The characteristics of our two cases of normotensive SRC were as follows: a recent onset of SSc, diffuse skin sclerosis, ILD, a high ANA titer, anti-Scl-70 antibody positivity, the elevation of serum CK and the presence of serositis. Thrombocytopenia was the first manifestation of TMA in both patients and occurred within 3 weeks (18 days in Case 1 and 16 days in Case 2) of starting GC treatment. The BP of each patient remained in the normal range and both patients were asymptomatic when the TMA developed. Although the TMA resolved within a month, the renal function of each patient continued to deteriorate for weeks to months.
afterward. This contrasts sharply with the characteristics of hypertensive SRC, in which renal function deteriorates rapidly and patients soon become oliguric. The prognosis for each patient was poor despite a prompt initiation of angiotensin-converting enzyme (ACE) inhibitor and plasma transfusion or plasma exchange. Both patients did not satisfy the classical definition of SRC (1) because they did not have accelerated hypertension.

Although accelerated hypertension is usually recognized as a feature of SRC, a subset of this condition lacking hypertension has also been reported (5), with 11% to 14% of SRC patients being normotensive (5, 6). Normotensive SRC patients have a higher frequency of microangiopathic hemolytic anemia, thrombocytopenia and pulmonary hemorrhage, have usually received high-dose GC therapy (≥30 mg of prednisone daily) within the 2 months preceding the renal crisis, and have a significantly lower survival rate than those patients with hypertensive SRC (5). Our cases had similar features to those in these previous reports, except that neither of our patients exhibited pulmonary hemorrhage.

SSc with ANCA-positive renal failure has also been reported as a subset of SRC (7). The condition is generally characterized by a longer disease duration, anti-Scl-70 antibody positivity, anemia, fever and pulmonary hemorrhage, but these patients are not necessarily normotensive (7). In fact, 32% of patients with ANCA-positive scleroderma renal disease have an elevated BP (>140/90 mmHg) (8). In contrast to patients with GC-induced normotensive SRC, the disease duration is longer (median of 7 years) and only a minority of patients (14%) have TMA. Rapidly progressive glomerulonephritis is common in SSc patients with ANCA-associated renal failure (83%).

Approximately half of all patients with SRC will develop TMA (6, 9, 10). Distinguishing SRC with TMA from thrombotic thrombocytopenic purpura (TTP), a condition which also occurs in SSc, is occasionally difficult based on laboratory findings alone. However, case reports of SSc complicated by TTP indicate that these patients have a fever and neurological deficits as well as TMA (11). ADAMTS13 activity has not been reported in most cases. In fact, ADAMTS13 is considered to be the most reliable marker of TTP, and typically ADAMTS13 activity shows a marked decrease in TTP patients (12). ADAMTS13 activity has not been fully investigated in SRC, although it might be useful for differentiating SRC from TTP. Our two patients had neither fever nor any neurological symptoms, and ADAMTS13 did not show a marked decrease. From these findings, the diagnosis of TTP was considered unlikely in both of our patients.

We reviewed the reported cases of normotensive SRC or SSc complicated by TMA in Japan, including those from Japanese language journals (13-17) (Table). Hypertensive SRC, ANCA-positive SRC and SSc complicated by TTP were excluded from our review. We found a total of 8 cases of normotensive SRC, including the 2 patients presented herein. All 8 of the patients fulfilled the original criteria for normotensive SRC (5), which are acute renal failure due to SSc and normal BP (diastolic BP ≤90 mmHg). The anti-Scl-70 antibody was positive in all of the patients, and the ANA titer was very high (≥1:5,120) in the 5 patients who were tested. With the exception of Patient 8, all of the patients had early SSc with diffuse skin sclerosis and developed TMA within one month of starting GC treatment. Serositis was present in 6 out of the 8 patients, and an elevation of the serum CK was found in 4 out of 5 cases. Pulmonary hemorrhage was observed in 2 patients (14, 17). Patient 8 was exceptional because she had longstanding diffuse SSc and then developed TMA with pericardial and pleural effusions while being treated with PSL at 7.5 mg/day. The prognoses were poor in most cases. Therefore, the normotensive SRC patients reported in Japan share both clinical and serological findings.

Previous reports have indicated that positivity for the anti-Scl-70 antibody is unrelated to SRC, whereas the anti-RNA polymerase III antibody is reported to be a predictor of SRC (1, 6). However, our review of 8 Japanese patients showed that they were all positive for the anti-Scl-70 antibody, while the anti-RNA polymerase III antibody was measured in 2 out of 8 patients and both were found to be negative. One of the major reasons for these differences is that almost all of the previous studies were conducted in patients with hypertensive SRC. It is not known whether anti-Scl-70 antibody or anti-RNA polymerase III antibody are risk factors for normotensive SRC because there have been no direct comparisons of the serological characteristics between hypertensive SRC and normotensive SRC. In addition, racial differences need to be considered.

ACE inhibitor therapy improves the survival of patients with hypertensive SRC (18). In contrast, the survival of Japanese patients with GC-induced normotensive SRC was very poor despite an intensive treatment with ACE inhibitors and plasma exchange. Hemodialysis was required in 5 out of the 8 patients, and 5 of the patients died within 3 months of the onset. The ADAMTS13 activity was measured in 4 patients, and it did not show a marked decrease. ADAMTS13 activity was normal or only moderately reduced in more...
than half of the patients with SSc and TMA (19), and this may explain the poor response of SSc patients with TMA to plasma exchange. Similarly, their normal BPs at the onset of the TMA may also explain their unresponsiveness to treatment with ACE inhibitors.

According to the original report on normotensive SRC, GC therapy was started within 2 months prior to the onset of renal failure in 13 out of 14 patients (5). The administration of GC was initiated for the treatment of myositis or pericarditis in 6 of these 13 patients. An elevated serum CK level and pericarditis were also frequent in Japanese patients. In a case series of Japanese SSc patients with pericardial effusion, one patient who had SSc overlapping with polymyositis developed pericardial effusion and normotensive renal failure after 4 months of PSL treatment for myositis (20). Naniwa et al. suggested that progressive skin thickening, overt pericardial effusion, malaise and myopathy are the prodromal signs of pulmonary-renal syndrome in SSc patients with TMA, and that high-dose GC therapy should not be given to such patients (17). Therefore, patients with diffuse skin sclerosis, early disease, myositis, pericarditis and serological findings such as a high ANA titer and...
positivity for anti-Scl-70 antibody may have an elevated risk of developing normotensive SRC secondary to GC therapy.

In conclusion, GC-induced normotensive SRC has distinctive clinical features in Japanese patients. The disorder typically develops within one month of starting GC treatment. Accordingly, GC therapy should be avoided in high risk patients. If GC treatment is unavoidable, then it would be prudent to use as low of a dose as possible with extreme caution. Frequent monitoring of the platelet count might be the quickest and most reliable method for detecting normotensive SRC.

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References