

# Delayed onset of posterior reversible encephalopathy syndrome in a case of scleroderma renal crisis with maintenance hemodialysis

## Case report and literature review

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### Abstract

**Introduction:** In some cases, scleroderma renal crisis (SRC) is not easily distinguishable from other thrombotic microangiopathies such as thrombotic thrombocytopenic purpura, especially when the presentation includes neurological or extra-renal manifestations. Here, we present a case of SRC who developed a rare neurotoxic complication, posterior reversible encephalopathy syndrome (PRES).

A 36-year-old man with a history of diffuse cutaneous systemic sclerosis developed SRC and acute-on-chronic renal failure and ultimately required maintenance hemodialysis. Three weeks after starting hemodialysis, the patient presented with confusion and a new-onset seizure disorder. Laboratory examinations revealed thrombocytopenia, a low haptoglobin level, and schizocytes on a blood smear. SRC-related PRES was considered first after PRES was confirmed by brain magnetic resonance imaging. Antihypertensive therapy comprising captopril and amlodipine was administered, and the patient experienced a complete neurological recovery 3 days later without plasma exchange. In all previously reported cases of SRC-associated PRES, PRES developed before hemodialysis. Our report is, therefore, the first to describe a case of onset of SRC-related PRES 3 weeks after the initiation of maintenance hemodialysis.

**Conclusion:** This case demonstrates that microangiopathy and extra-renal manifestations can develop even in SRC patients with end-stage renal disease and that these manifestations can be successfully managed with angiotensin-converting enzyme inhibitors (ACEIs) and aggressive blood pressure control. We recommend continuing ACEI therapy if elevated blood pressure persists after maintenance hemodialysis.

**Abbreviations:** ACEI = angiotensin-converting enzyme inhibitors, ADAMTS13 = a disintegrin and metalloprotease with thrombospondin type 1 motif 13, CT = computed tomography, FLAIR = fluid-attenuated inversion recovery, MAHA = microangiopathic hemolytic anemia, MRI = brain magnetic resonance imaging, PRES = posterior reversible encephalopathy syndrome, SRC = scleroderma renal crisis, SSc = systemic sclerosis, TTP = thrombotic thrombocytopenic purpura.

**Keywords:** case report, hemodialysis, microangiopathy, posterior reversible encephalopathy syndrome, scleroderma renal crisis, seizure

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This case report did not require an ethics committee approval according to the current laws in our Hospital, and patient's informed consent could not be obtained because the patient died due to progression of the disease before we wrote the case report.

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## 1. Introduction

Patients with the disease systemic sclerosis (SSc) present with skin thickening in the presence or absence of systemic organ involvement. When associated with renal failure, SSc is a well-known cause of scleroderma renal crisis (SRC), which is characterized by severe arteriole thickening in association with elevated blood pressure and increased renin levels. SRC has also been associated with microangiopathy and neurologic manifestations, including headache, disturbed consciousness, and seizure.<sup>[1]</sup> Although the pathogenesis of SRC differs from those of other microangiopathies such as thrombotic thrombocytopenic purpura (TTP), the conditions share the potential for neurological or renal manifestations. It is, therefore, difficult to diagnose SRC without testing for deficiency in the activity levels of the von Willebrand factor cleaving protease a disintegrin and metalloprotease with thrombospondin type 1 motif 13 (ADAMTS13), which is characteristic of idiopathic TTP.<sup>[2]</sup>

The posterior reversible encephalopathy syndrome (PRES) is a syndrome characterized by the presentation of neurotoxic symptoms and typical neuroimaging finding of vasogenic cerebral edema.<sup>[3]</sup> Many diseases can cause PRES, including malignant hypertension, eclampsia, and vasculitis, and certain immunosuppressive drugs may also be causative. The proposed

pathogenesis of PRES involves hypertension-induced brain hyperfusion and vasculopathy, similar to SRC. However, PRES is rarely reported in patients with SSc; to date only 4 cases of SSc-related PRES, including 2 cases of SRC-related PRES, have been reported. Here, we present a patient with SRC who developed PRES after 3 weeks of maintenance hemodialysis.

## 2. Case presentation

The 36-year-old male patient in this case had a 6-year history of diffuse cutaneous SSc (Fig. 1) and had not received regular follow-up or medication therapy. He had experienced malaise, poor appetite, and progressive shortness of breath for 1 month and oligouria for 3 days. He was admitted to our hospital with renal failure and pulmonary edema. In the emergency department, his blood pressure, pulse rate, and respiratory rate were 174/127 mm Hg, 88/min, and 22/min, respectively. Laboratory analysis revealed the following values: white blood cell count, 7730/ $\mu$ L (3500–11,000/ $\mu$ L); hemoglobin, 8.6 g/dL (12–16 g/dL); platelet count, 87000/ $\mu$ L (150,000–400,000/ $\mu$ L); blood urea nitrogen, 78 mg/dL (6–21 mg/dL); creatinine, 8.9 mg/dL (1.1–1.5 mg/dL); calcium, 8.2 mg/dL (8.8–10.3 mg/dL); phosphorus, 5.4 mg/dL (2.7–4.5 mg/dL); haptoglobin, <6.56 mg/dL (30–200 mg/dL); and lactate dehydrogenase, 547 U/L (106–211 U/L). A routine urinalysis revealed a proteinuria score of 2+ (200 mg/dL), white blood cell count of 3–5/high power field, and red blood cell count of 25–50/high power field. The autoimmune profile indicated an antinuclear antibody level of 1:320 (speckles; normal, <1:40). Tests for anti-Scl70, anti-double-stranded DNA, anti-Ro, anti-La, and anticardiolipin antibodies were all negative. Kidney echogram showed a decreased bilateral kidney size without hydronephrosis. Despite the chronic changes visible on the echogram, the patient had developed acute pulmonary edema and oligouria only 3 days before admission. Accordingly, a clinical diagnosis of acute-on-chronic renal failure was made.

A further diagnosis of SRC was supported by the presence of renal failure with microangiopathic hemolytic anemia and hypertension, and the patient was started on captopril therapy. The sustained deterioration in renal function and anuria had led to a requirement for regular hemodialysis from admission. After 3 days, captopril was changed to amlodipine because the patient developed a severe, intolerable cough thought to be associated



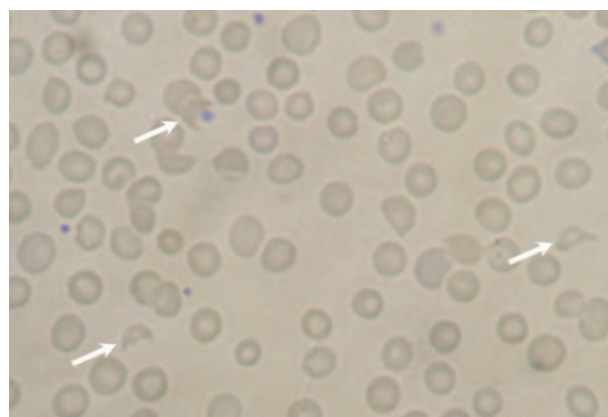
**Figure 1.** Image of the patient's hand, exhibiting shiny, thick skin with interphalangeal joint flexion contracture.

with captopril. His systolic blood pressure was controlled between 140 and 180 mm Hg. At approximately 3 weeks after the initiation of maintenance hemodialysis, the patient newly developed a generalized tonic-clonic seizure disorder. A brain computed tomography (CT) scan revealed a small lacunar infarct over the left basal ganglion without intracranial hemorrhage or large infarct. The seizure resolved spontaneously without anticonvulsants, and the patient was finally discharged home without incident and scheduled for regular hemodialysis thrice weekly.

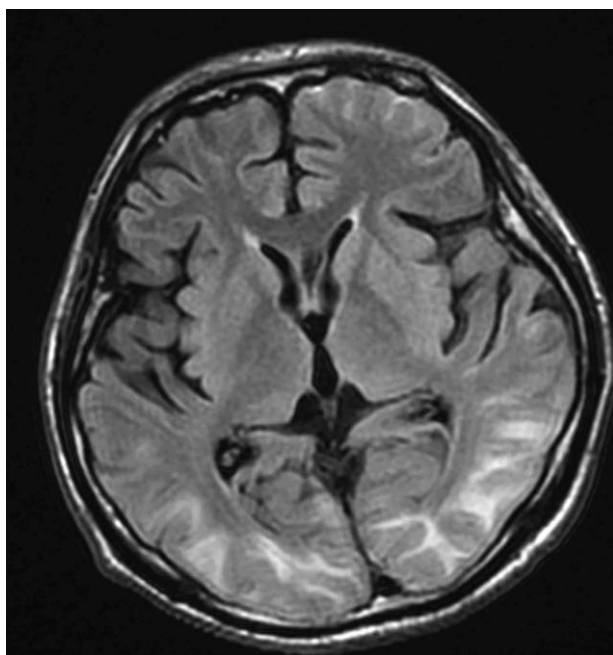
However, at 1 week after discharge, the patient developed a sudden-onset headache and vomiting with confusion and recurrence of the generalized tonic-clonic seizure. He presented at the emergency department with a blood pressure of 183/100 mm Hg, platelet count of 149,000/ $\mu$ L, serum LDH of 332 U/L, and a peripheral blood smear containing 2–3 schizocytes/HPF (Fig. 2). Brain CT revealed no interval change, and lumbar puncture revealed traumatic tapping only. Cerebrospinal fluid cultures were negative for bacteria, mycobacteria, and viruses. Brain magnetic resonance imaging (MRI) showed bilateral hyperintensity in the occipital and parietal lobes on a fluid-attenuated inversion recovery (FLAIR) sequence (Fig. 3). Finally, the patient was diagnosed with PRES. We resumed captopril therapy at a dose of 25 mg thrice daily. As it was difficult to differentiate SRC from TTP, we also considered plasma exchange treatment. However, the patient's mental status returned to normal within 3 days in the absence of plasma exchange, and a follow-up MRI of the brain 2 months later showed complete resolution of cerebral edema (Fig. 4). Therefore, SRC-related PRES was confirmed. Although the patient experienced a full neurologic recovery, his renal function did not improve and he remained dialysis dependent.

## 3. Discussion

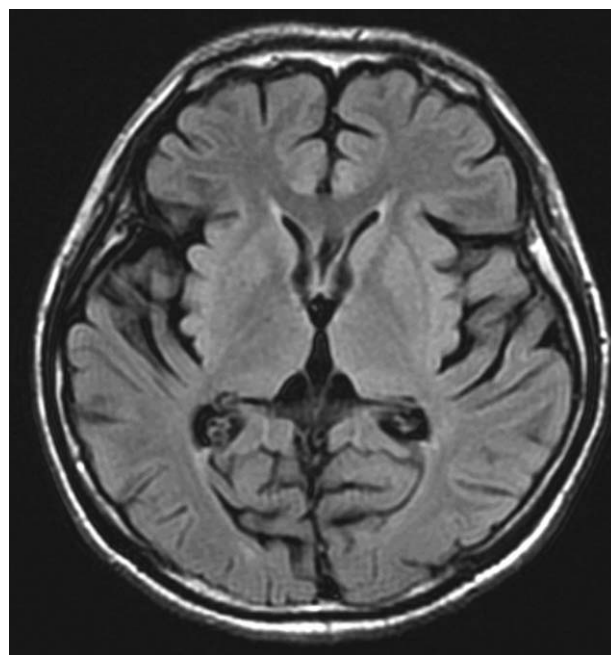
SSc is a multisystem disease involving the skin and internal organs, and is characterized by variable degrees of fibrosis in affected tissues and obliterative vasculopathy. SRC is a life-threatening complication that occurs in 5% of cases of SSc<sup>[1]</sup> and is characterized by clinical features such as high blood pressure, elevated renin levels, and renal failure. Diffuse skin involvement, corticosteroid use, and the presence of anti-RNA polymerase III antibodies have been identified as risk factors for SRC in patients



**Figure 2.** Peripheral blood smear performed during the second seizure attack indicated the presence of 2–3 schizocytes (arrows)/high power field (HPF). HPF = high power field.



**Figure 3.** Magnetic resonance imaging was performed 4 days after seizure onset. The representative image shows bilateral cerebellar hyperintensity, as well as hyperintensity in the occipital and parietal subcortical white matter on a fluid-attenuated inversion recovery (FLAIR) sequence. FLAIR = fluid-attenuated inversion recovery.



**Figure 4.** Abnormal fluid-attenuated inversion recovery (FLAIR) magnetic resonance imaging, performed 2 months after the imaging described in Figure 3, indicated the complete resolution of the brain changes. FLAIR = fluid-attenuated inversion recovery.

with SSc.<sup>[1]</sup> Microangiopathic hemolytic anemia and encephalopathy may also occur in patients with SRC.

As noted in the *Introduction*, it is difficult to differentiate SRC from other thrombotic microangiopathies, especially TTP. Although some cases of TTP have been reported in patients with SSc, only a few reported ADAMTS13 activity data, without which the differentiation of these conditions remains challenging.<sup>[4]</sup> A previous study found relatively lower ADAMTS13 activity in 87 patients with SSc, compared to those in a healthy control group; however, none of the patients with SSc had ADAMTS13 activity levels below 10% of the normal range, a typical finding of TTP, and none had detectable levels of anti-ADAMTS13 autoantibodies.<sup>[5]</sup> Although no studies have directly compared ADAMTS13 activity levels between patients with SRC and TTP, the finding of a very low ADAMTS13 level may help to confirm a diagnosis of TTP. In the present case, we did not check our patient's ADAMTS13 activity level; however, his complete neurologic recovery without plasma exchange favored the diagnosis of SRC.

PRES was first described in 1996 as a disease characterized by neurologic symptoms, including headache, blurred vision, altered consciousness, and seizure.<sup>[6]</sup> The typical neuroimaging finding of PRES is vasogenic cerebral edema with a primarily symmetrical distribution in the posterior lobes, including the occipital and parietal lobes. PRES may occur in association with a variety of diseases, including hypertensive encephalopathy, preeclampsia/eclampsia, connective tissue disease, and TTP, as well as during treatment with immunosuppressive drugs (e.g., cyclosporine) and bone marrow transplantation, and is usually reversible once the underlying etiology is identified and treated, along with blood pressure reduction.<sup>[3,7,8]</sup> There are 2 main hypotheses regarding the mechanism of PRES. According to the first, severe hypertension-induced cerebral hyperperfusion leads to autor-

egulation failure and vasogenic edema; in the second, systemic toxicity or vasculopathy causes brain hypoperfusion even in the absence of malignant hypertension, leading to increased endothelial permeability and brain edema.<sup>[8]</sup>

In a summary of 13 cases of PRES related to connective tissue disease, Min et al<sup>[9]</sup> described 10 patients with systemic lupus erythematosus (SLE), 2 with Wegner's granulomatosis, and 1 with SSc and identified possible risk factors, including malignant hypertension and previous use of cyclophosphamide or cyclosporine. Through a comprehensive search of Medline, we identified only 4 reported cases of SSc-related PRES<sup>[10-13]</sup> and compared the features of these cases with those of our presenting case (Table 1). The mean age of the 5 patients was 33.2 (27-39) years, and the initial presentations were relatively similar and included confusion, blurred vision, and seizure. The mean arterial blood pressure at presentation was 140.6 (123-173) mm Hg. Two patients had diffuse cutaneous SSc, 1 had limited cutaneous SSc, 1 had SSc/SLE overlap syndrome, and 1 had unknown-type SSc, although this latter patient exhibited anti-Scl 70 antibody positivity, a marker of diffuse cutaneous SSc.<sup>[13]</sup> Three of the 5 patients developed microangiopathic hemolytic anemia (MAHA), whereas the patient with SSc/SLE overlap syndrome did not have MAHA; in that case, intravenous pulse cyclophosphamide was considered the main risk factor. Because 4 of the 5 identified patients had renal failure, we hypothesized that SRC might also be a risk factor for PRES.

We note that treatments and outcomes of SSc-related PRES differ from those of TTP, and that all 5 patients in the reported cases experienced a neurologic recovery without plasma exchange. In the 2 previously reported cases of SRC-related PRES, the onset occurred earlier than in our case; specifically, both patients developed PRES before hemodialysis initiation,<sup>[10-11]</sup> whereas the patient in our case developed PRES

**Table 1****A comparison of reported cases of systemic sclerosis-related posterior reversible encephalopathy syndrome (PRES).**

Author (y)	Age/ sex	Type of SS	Symptoms	Possible risk factors	Renal function (Cr mg/dL)	Initial BP (mm Hg)	=MAHA	Treatment	Outcomes
Poon and Mok (2005) <sup>[10]</sup>	34/ male	Limited SS	Confusion seizure	MH SRC	ARF 0.97 -> 5.59	240/ 140	+	Control BP (ACEI) Hemodialysis	Neurology: recovered renal: Not mention
Yong et al (2003) <sup>[11]</sup>	39/ female	SS/ SLE	Blur vision Seizure	Pulse cyclophosphamide	ARF Cr: N/A	170/ 100	N/A	Control BP (nitrates, prostacyclin)	Neurology: recovered Renal: recovered
Pinol et al (2010) <sup>[12]</sup>	27/ male	Diffuse SS	Confusion, blur vision	MH SRC	ARF Cr: N/A	190/ 110	+	Control BP (Captopril)	Neurology: Recovered Renal: recovered
Hounoki et al (2011) <sup>[13]</sup>	30/ female	N/A	Blur vision Nausea/vomiting Seizure	MH	No 0.5	140/ 120	N/A	Control BP (Captopril Candesartan)	Neurology: Recovered Renal: not mention
Our case	36/ male	Diffuse SS	Confusion Seizure	MH SRC	ESRD 8.9	174/ 127	+	Control BP (Captopril, amlodipine)	Neurology: Recovered Renal: Maintenance hemodialysis

ACEI=angiotensin converting enzyme inhibitor, ARF=acute renal failure, BP=blood pressure, Cr=creatinine, ESRD=end-stage renal disease, MH=malignant hypertension, N/A=not available, N/A=not available, SLE=systemic lupus erythematosus, SRC=scleroderma renal crisis, SS=systemic sclerosis.

at 3 weeks after the initiation of maintenance hemodialysis. This suggests that SRC-related microangiopathic damage to the central nervous system may persist even after a patient becomes dialysis-dependent. Currently, the angiotensin-converting enzyme inhibitor (ACEI) therapy is the mainstay for SRC, and we recommend continuing ACEI therapy for blood pressure control even in dialysis-dependent patients.

#### 4. Conclusion

SSc associated with PRES is a very rare condition that is difficult to differentiate from TTP. SRC is a risk factor for PRES because of its association with hypertension and microangiopathy, both of which are pathogenic factors for PRES. Our case demonstrates that PRES can occur in patients with SRC even after the initiation of maintenance hemodialysis. Therefore, we recommend that patients with SSc continue ACEI therapy if hypertension and evidence of microangiopathy persist during maintenance hemodialysis.

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