Case Report

Scleroderma Renal Crisis after Steroid Therapy in Interstitial Lung Disease, as Initial Presentation in a Limited Cutaneous Scleroderma Patient: Case Report

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This case report of a 70-year-old Thai female with type 2 diabetes and essential hypertension who presented with dyspnea, rapidly declining of kidney function, malignant hypertension, and thrombotic microangiopathy after a two-week course of high-dose corticosteroid administration for interstitial lung disease (ILD). A physical examination revealed characteristics compatible with limited cutaneous systemic sclerosis (lcSSc). However, SSc was not diagnosed at the time the patient's ILD discovered. Laboratory investigations showed proteinuria with microscopic hematuria, the presence of anti-topoisomerase I antibodies, high titer of antinuclear antibodies, and low serum of complement C3 and C4. The diagnosis required differentiation between severe proliferative type of lupus nephritis and scleroderma renal crisis, as treatment for these two diseases differs greatly. Thus, the patient underwent percutaneous kidney biopsy, and the renal pathology revealed an onion-skin appearance with fibrinoid necrosis at the arterioles and arteries. The final diagnosis was lcSSc with scleroderma renal crisis.

Keywords: Scleroderma renal crisis, Limited cutaneous scleroderma, Systemic sclerosis

J Med Assoc Thai 2019;102(6):724-8
Website: http://www.jmatonline.com
Received 19 Jul 2018 | Revised 25 Mar 2019 | Accepted 29 Mar 2019

Systemic sclerosis (SSc) is a connective tissue disease characterized by skin fibrosis. It is classified mainly into two types, limited cutaneous systemic sclerosis (lcSSc) and diffuse cutaneous systemic sclerosis (dcSSc)[1]. Scleroderma renal crisis (SRC) is a rare but serious complication that often has poor clinical outcomes, including dialysis dependency and high mortality[2,3]. The incidence of SRC in cases of dcSSc is approximately 2% to 15%(4). However, the development of SRC in cases of lcSSc is extremely rare, with an incidence of 0.5% to 0.6%[4]. In Thailand, the overall prevalence of SRC in cases of SSc was 0.85%[5]. Previous studies have reported risk factors for developing SRC included corticosteroids usage of more than 20 mg/day, rapid progression of skin tightness, tendon friction rubs as detected through physical examination, and the presence of anti-RNA polymerase III antibodies[1,6].

The interstitial lung disease (ILD) is a frequent manifestation in SSc and is more common in dcSSc patients than in those with lcSSc. The prevalence varies depending on the measures used in diagnosis but is up to 90% according to diagnosis by high-resolution computed tomography (HRCT)[7]. ILD can be the first presentation in 3.3% of SSc patients with unrecognized symptom of Raynaud's phenomenon[8]. Here, the authors reported a patient with lcSSc first presented with ILD, was treated with corticosteroid, and subsequently developed SRC. The present study was approved by the Khon Kaen University Ethics Committee for Human Research (HE601005).

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Case Report

A 70-year-Thai female came to a local hospital after having suffered from progressive dyspnea and non-productive cough without fever for two months. She had markedly limited functional activity

How to cite this article: Tonsawan P, Chan-on C, Puapairoj A, Suwannaroj S. Scleroderma Renal Crisis after Steroid Therapy in Interstitial Lung Disease, as Initial Presentation in a Limited Cutaneous Scleroderma Patient: Case Report. J Med Assoc Thai 2019;102:724-8.

(Class III according to the New York Heart Association Classification). Her past medical history showed she had suffered from well-controlled uncomplicated type 2 diabetes and essential hypertension. HRCT of the patient's chest was conducted. The findings showed a ground-glass appearance at both lower lungs and multiple sub-centimeter mediastinal nodes. A diagnosis of ILD and usual interstitial pneumonia was made. There was no record of the presence of the skin signs of scleroderma at the time of ILD diagnosis.

She was prescribed 30 mg/day of corticosteroids. Two weeks later, she developed progressive dyspnea, limb edema, and decreased urine volume. She was referred to a University Hospital. On the admission date, her physical examination revealed blood pressure of 190/86 mmHg, tachypnea, moderately anemia, bibasilar crackles, and pitting edema of both limbs. Basic laboratory investigations revealed hemoglobin of 6.6 g/dL, white blood cell count of 5,440 cell/mm^3, and platelet count of 26,000 cell/mm^3. A peripheral blood smear showed microangiopathic hemolytic anemia (MAHA). Blood urea nitrogen and serum creatinine were 45.8 mg/dL and 3.3 mg/dL (baseline 1.2 mg/dL), respectively. Her serum lactate dehydrogenase (LDH) level was 1,362 U/L (normal 89 to 221), and fibrinogen level was 128 mg/dL (normal 200 to 363). The results of a coagulation test were normal. She was diagnosed with acute kidney injury and malignant hypertension with thrombotic microangiopathy (TMA).

Physical examination and investigation to identify causes of TMA revealed puffy fingers, a slight tightening of the skin at the face and forearm proximally to elbow, a salt-and-pepper appearance at the forehead, and abnormal nailfold capillaries. The investigation also demonstrated total urinary proteinuria excretion was 0.7 g/day with sediment contained 5 to 10 of red blood cells/high power field (HPF). In addition, a test for antinuclear antibodies was positive (titer was 1:2,560 for nucleolar and speckle patterns). The serum level of complement component 3 (C3) was 43.8 mg/dL (normal 60 to 140), and of complement component 4 (C4) was 6 mg/dL (normal 16 to 40). The levels of a disintegrin and metalloproteinase with thrombospondin type I motif, member 13 (ADAMTS13) was normal activity. A test for anti-topoisomerase I (anti-Scl 70) antibodies was positive. Tests for anti-U1-nuclear ribonucleoprotein (anti-U1-RNP) antibodies, anti-proteinase 3 (anti-PR3) antibodies, anti-myeloperoxidase (anti-MPO) antibodies, lupus anticoagulant, anti-cardiolipin antibodies, anti-beta-2 glycoprotein antibodies, and anti-double stranded DNA (anti-dsDNA) antibodies were negative.

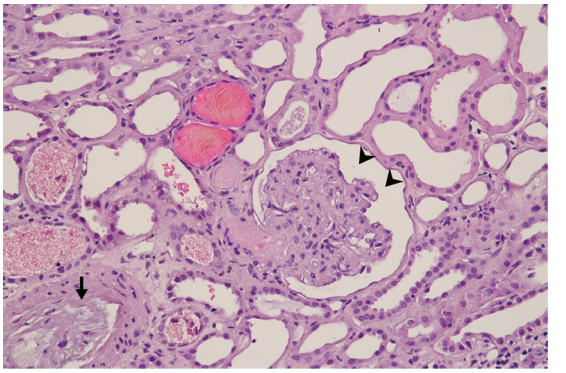

Figure 1. This lesion consists of thrombus in the interlobular artery (arrow), bloodless glomeruli (arrowhead), and flattening and dilatation of the renal tubule (hematoxylin and eosin stain, original magnification ×400).

A diagnosis of SSc was made according to the 2013 guideline laid out by the American College of Rheumatology (ACR) and the European League Against Rheumatism (EULAR) with clinical of lcSSc[9]. In the present case, serum levels of complement C3 and C4 were low. Thus, the etiology of the patient's acute kidney injury had to be distinguished between a severe proliferative type of lupus nephritis (LN) and SRC. Because the treatment for severe LN and that for SRC are substantially different, a renal pathological diagnosis was needed. The patient subsequently underwent kidney biopsy after blood and platelet transfusion brought them back into their normal ranges.

Renal pathology

Renal pathology using light microscopy revealed nine glomeruli. The bloodless glomeruli with diffuse acute tubular necrosis were observed (Figure 1). There were no karyorrhexes, wire loops, or hyaline thrombi. There was fibrinoid necrosis and fibrin thrombi in the arterioles and arteries (Figure 1-3), and the blood vessels had an onion-skin appearance with intimal hyperplasia (Figure 4). In addition, some glomeruli demonstrated mild focal increase in the mesangial cells and matrix (Figure 2).

The immunofluorescence examination of seven glomeruli revealed negative for IgG, IgM, IgA, C3, C4, C1q, kappa, lambda, and fibrin. Accordingly, the main diagnosis was diabetic nephropathy with SRC.

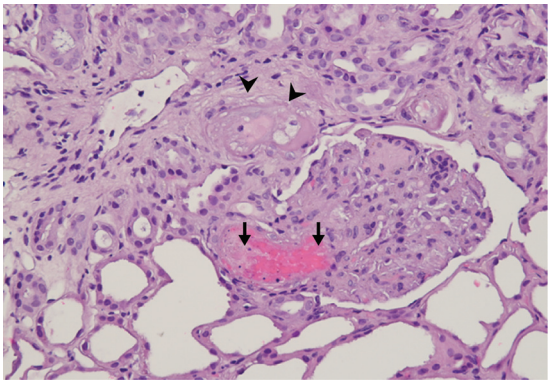

Figure 2. This glomerulus had mild segmental mesangial matrix expansion, fibrin thrombi (arrowhead), fibrinoid necrosis (arrow) of the arteriole that extended to the glomerulus (arrow), and flattening and dilatation of the renal tubules (hematoxylin and eosin stain, original magnification ×400).

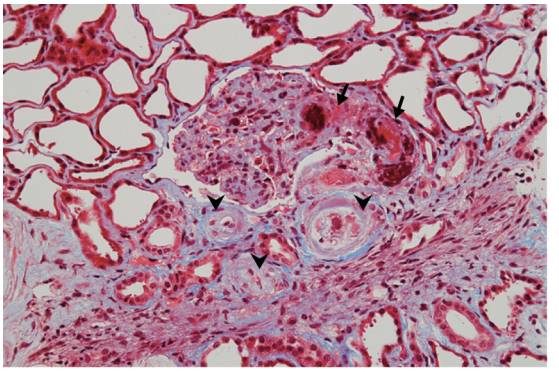

Figure 3. This figure illustrates fibrinoid necrosis and fibrin thrombi in glomeruli and arterioles (arrow), as well as mucoid intimal thickening in arterioles (arrowhead; Masson's trichrome, original magnification ×400).

During admission, the patient experienced oliguria with fluid overload and required hemodialysis. She subsequently developed hospital-acquired pneumonia and respiratory failure. After renal biopsy had been conducted and SRC diagnosed, angiotensin-converting enzyme inhibitors were not prescribed due to the patient's hemodynamically instability. She eventually died from septic shock with severe metabolic acidosis.

Discussion

The major causes of TMA are primary thrombotic thrombocytopenic purpura (TTP), hemolytic uremic syndrome (HUS), disseminated intravascular

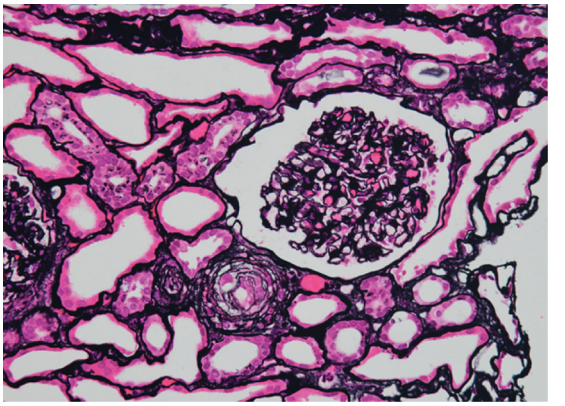

Figure 4. This figure shows the lamellated onion-skin appearance of the arteriole (Jones' Silver Stain, original magnification ×400).

coagulation (DIC), drug-induced, malignancy, autoimmune disease (particularly systemic lupus erythematosus with antiphospholipid syndrome), and scleroderma renal crisis[10]. In the present case, the presence of typical skin signs for lcSSc and a specific antibody associated with SSc fulfilled the criteria for lcSSc diagnosis with ILD as internal organ involvement[11]. This underlying condition caused dyspnea and brought the patient to the hospital. Additionally, the presence of anti-topoisomerase-I both assisted in the diagnosis of SSc and is associated with pulmonary fibrosis[12].

After high-dose corticosteroid exposure, the clinical evidence of TMA and acute kidney injury together with fibrinoid necrosis and the onion-skin appearance in the arterioles and small arteries in the kidney suggested that this was a classic case of SRC[13]. In addition, other causes of TMA were excluded. The normal protease activity of ADAMTS13 meant that TTP-HUS was unlikely[10]. Coagulogram results were normal. Meanwhile, the patient had a severe condition that indicated possible DIC[14]. The final diagnosis was lcSSC with SRC. There are many risk factors for SRC, a major one is having received a high dose of corticosteroids[2,15]. In the present patient, SRC was determined to have developed after corticosteroid treatment, rather than with the onset of ILD.

It is atypical to find low levels of serum C3 and C4 complement, as were found in the present patient, in cases of SRC. Interestingly, prior studies have found that hypocomplementemia in some SSc patients. The finding might be associated with SSc-overlap diseases, SSc disease activity, and internal organ such as heart and pulmonary involvement[16-18]. Previous studies

have also reported that anti-RNA polymerase III antibody is strongly associated with SRC, indicating that testing for anti-RNA polymerase III should be a part of the diagnostic work up in patients presenting with TMA from unknown causes[19-21]. Unfortunately, this test was unavailable in this case.

In general, SRC is determined by clinical diagnosis. Kidney biopsy should be considered to rule out other causes and provide prognosis in case of uncertain diagnosis[13]. In the present case, a biopsy was performed to distinguish between a severe proliferative type of lupus nephritis and SRC because the patient had low serum complement.

ILD is primarily the result of inflammation; hence, the immunosuppressive agents are the treatment of choice. Despite the administration of corticosteroids being a treatment option in ILD, it carries an important risk of developing SRC. Thus, the risks and benefits of corticosteroid usage in patients with SSc should be properly weighted. Steroid-sparing agents such as cyclophosphamide, mycophenolate mofetil, and azathioprine should be used to avoid the development of SRC[22].

ILD is a common a presentation of SSc, particularly in cases of dcSSc in which anti-topoisomerase-I antibodies are present[22]. ILD as a first presentation prior to skin change is very rare, especially in cases of SRC development in patients with lcSSc[4,8]. Therefore, the other possible diagnosis in the present patient was early dcSSc, which first manifested as ILD and developed into SRC after corticosteroid administration was conducted as treatment for the patient's ILD[23].

Once ILD is diagnosed, the secondary causes of the condition should be observed and investigated further. This includes extensive physical examination looking for signs of SSc and tests for scleroderma-specific autoantibodies, those are anti-centromere antibodies, anti-topoisomerase-I (anti-Scl 70) antibodies, and anti-RNP polymerase III antibodies[24].

Conclusion

Scleroderma renal crisis is a severe complication with high mortality rate in SSc patients. ILD might be the first presentation of SSc; hence, patients with ILD should be examined for clinical signs of SSc and scleroderma-specific autoantibodies. Scleroderma renal crisis is common in patients with lcSSc. One important risk factor for developing SRC is high-dose corticosteroid administration. A corticosteroid-sparing regimen is an alternative for treatment of ILD in SSc patients.

What is already known on this topic?

Scleroderma renal crisis is a serious complication of SSc and more commonly occurs in patients with dcSSc than those with lcSSc. The classic manifestations of SRC are rapidly declining kidney function, accelerated or abrupt onset hypertension, and TMA. High dosage corticosteroid therapy is a common precipitating cause. ILD is a clinical presentation of SSc and is associated with the presence of positive anti-topoisomerase I antibodies.

What this study adds?

ILD might be the first presentation of lcSSc. In cases ILD is suspected, the authors would like to recommend closely examining the patient for signs of SSc and scleroderma-specific autoantibodies prior to initiate corticosteroid treatment. If the patient was diagnosed as SSc, treatment with the corticosteroid-sparing agents should be considered to prevent the development of SRC. Additionally, the present case demonstrated low serum complement C3 and C4 levels. This is an uncommon presentation but can be observed in cases of pure SSc and might be associated with severe disease. However, SSc-overlap syndrome and other causes should also be excluded.

Acknowledgement

The authors would like to thank Dr. Dylan Southard for editing the manuscript under the Research Affairs Publication Clinic at Khon Kaen University Faculty of Medicine.

Conflicts of interest

The authors declare no conflict of interest.

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