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# Case report of systemic sclerosis: Uncommon manifestation of nephrotic syndrome post-renal crisis

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**Abstract**

Kidney involvement in systemic sclerosis occurs in about 20% of cases, with scleroderma renal crisis as a significant complication. However, cases of glomerular disease with massive proteinuria are rare. We present a unique case of systemic sclerosis with the development of nephrotic syndrome. The report provides clinical details and podocyte pathological findings. A 40-year-old male with prior skin sclerosis was diagnosed with systemic sclerosis. Treatment with oral prednisone led to gradual improvement, but a year later, he experienced a systemic sclerosis renal crisis. Using the angiotensin converting enzyme (ACE) inhibitors improved kidney function. However, 3 months later, nephrotic syndrome was diagnosed. Despite an increased prednisolone dose, proteinuria persisted. A kidney biopsy revealed glomerular sclerosis and characteristic vascular changes. Immunofluorescent studies showed no deposits. Electron microscopy confirmed podocyte abnormalities.

**Keywords**

Systemic sclerosis, nephrotic syndrome, vasculopathy

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## Introduction

Systemic sclerosis is an autoimmune disease characterized by immune dysregulation that causes vascular dysfunction and multiple organ failure with progressive fibrosis of various organs. There are reported various kidney disorders associated with systemic sclerosis. Kidney involvement is detected in approximately 20% of cases with systemic sclerosis. Systemic sclerosis renal crisis is one of the major kidney complications of systemic sclerosis and is characterized by a rapid decrease in glomerular filtration rate.[1] In addition, thrombotic kidney disease was also reported and may cause renal dysfunction.[2] However, glomerular disease with massive proteinuria is rarely observed in systemic sclerosis. This systemic sclerosis case developed nephrotic syndrome during the disease. We will present a case together with the pathological findings of podocytes.

## Case

A 40-year-old man visited our hospital with bilateral lower leg edema. The patient had skin sclerosis around 6 years ago. Although anti-Scl-70 (topoisomerase I) antibody and anti-centromere antibody were negative, systemic sclerosis was diagnosed based on the clinical symptoms and pathological findings of the skin. Oral prednisone (30 mg/day) was started for skin sclerosis by a dermatologist. The skin sclerosis gradually improved, and the steroid dose was reduced gradually. One year before his admission, while he was on a daily 5-mg dose of steroids, his blood pressure was increased to 220/130 mmHg, and vascular findings of the retina were Keith-Wagener III. He had 1+ proteinuria and 0.12 g/gCr quantitatively. In the urinary sediment, there are no red blood cells, granular nor cellular casts. His serum creatinine was elevated to 1.29 mg/dL, while maintaining a stable hemoglobin level of 14.9 g/dL He was diagnosed with renal crisis

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of systemic sclerosis. He started antihypertensive treatment with an ACE inhibitor and Ca channel blocker, and his kidney function and blood pressure improved. Nevertheless, 3 months after the episode of renal crisis, proteinuria gradually increased. Urinalysis showed 4+ proteinuria and 4.24 g/day quantitatively, the patient's serum creatinine and serum albumin levels were 1.06 mg/dL and 2.8 g/dL, respectively. Then, he was diagnosed with nephrotic syndrome and admitted to our hospital for further examination. Physical examination revealed mild pallor of the eyelid conjunctiva and bilateral indurated edema of the lower legs. His physical conditions included skin thickening of the fingers, extending proximal to the metacarpophalangeal joints, and abnormal nailfold capillaries, resulting in a 13-point score on the 2013 ACR/EUAR scale.

Laboratory data at admission showed white blood cells 12,900 $mm^3$, hemoglobin 12.3 g/dL, hematocrit 39.5%, and plateletes $45.8 \times 10^3/\mu L$. Other laboratory data showed serum creatinine 1.05 mg/dL, blood urea 12 mg/dL, aspartate aminotransferase (AST) 24 IU, alanine aminotransferase (ALT) 13 IU, creatine phosphokinase (CPK) 106 IU/L, and lactate dehydrogenase (LDH) 229 IU/L. Anti-Scl-70 antibody, anti-centromere antibody, and anti-RNA polymerase III antibodies were negative, as well as antinuclear antibodies. Urinalysis showed proteinuria 4+ and the selectivity index was 0.05. Additionally, immune system showed no hypocomplementemia and antinuclear antibodies were negative. Infections (HIV, viral hepatitis C) and tumor markers were also negative. Additionally, there were no abnormalities in hormone metabolism, including diabetes mellitus. A kidney biopsy was performed on the 2nd day of admission. Light microscopy images revealed that 4 out of 22 glomeruli were glomerular sclerosis. Other glomeruli seemed to be normal. The vascular endothelium was swollen and is compatible with pathological findings for the renal crisis of systemic sclerosis (Figure 1). Immunofluorescent studies show no immunoglobulin or complement deposition. Electron microscopy showed effacement of the foot processes of glomerular epithelial cells, but there were no deposits in the subepithelial and/or mesangial areas (Figure 2). Electron microscopy confirmed endothelial cell swelling at the arteriole. The dose of prednisolone was increased to 20 mg/day for the treatment of nephrotic syndrome, but the proteinuria did not decrease. He was followed up at close intervals, but there were no crises, and no remission of the proteinuria was observed even after 6 months.

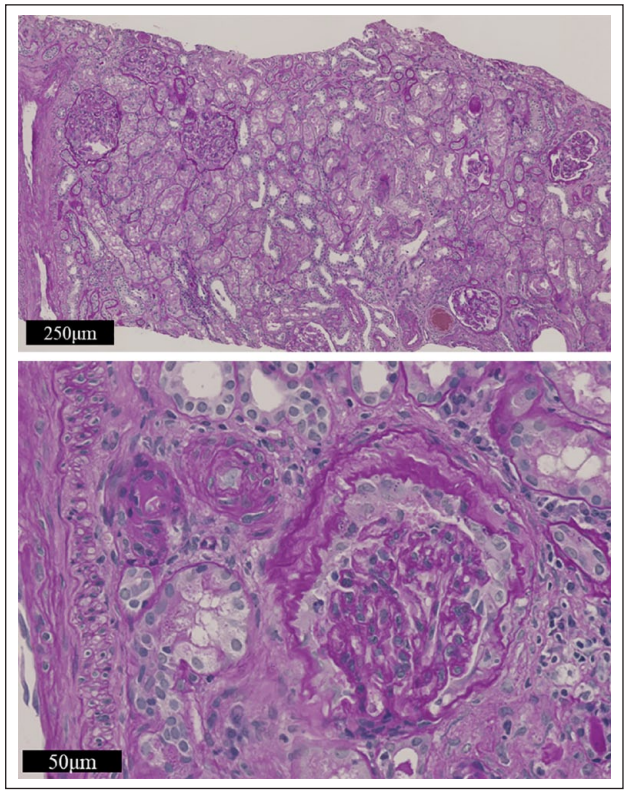


**Figure 1.** Despite some inflammatory cell infiltration, the tubules and interstitium were relatively preserved. Thickening and tortuosity of the glomerular basement membrane and glomerular atrophy were observed. In addition, there was edematous thickening of the intima-media of the arterioles (Periodic Acid Schiff stain).

## Discussion

We reported a case of nephrotic syndrome that developed after the renal crisis of systemic sclerosis. There was no deposition of immunoglobulin in the glomerulus, but swelling of the glomerular endothelial cells and loss of foot processes of podocytes were observed. Systemic sclerosis is often associated with various renal lesions and exhibits decreased glomerular filtration, but it is rarely manifested as nephrotic syndrome.

In this nephrotic case, there was no immunoglobulin complement deposition in the glomerulus, the laboratory data showed high selectivity in protein excretion in urine. Glomerular endothelial cell swelling and foot process effacement of podocytes were observed. It is known that the podocytopathy is induced by other immune complex diseases, anti-phospholipid syndrome, infections (HIV, viral hepatitis C), diabetes mellitus, or medications.[3] Thus, his clinical data did not reveal the damage of podocytopathy.

Pathological findings were compatible with minimal change in nephrotic syndrome. However, the response to steroid treatment was poor. Wagner et al.[4] demonstrated in a rat ischemia-reperfusion model that renal ischemia induces dynamic changes in the molecular interactions between slit diaphragm proteins, leading to podocyte damage and proteinuria. Moreover, it is reported that ischemia decreased the slit diaphragm binding proteins, such as Neph1 and ZO-1, and induced massive proteinuria.[5] These pathological changes are like pathological findings of minimal change nephrotic syndrome. These mechanisms seem

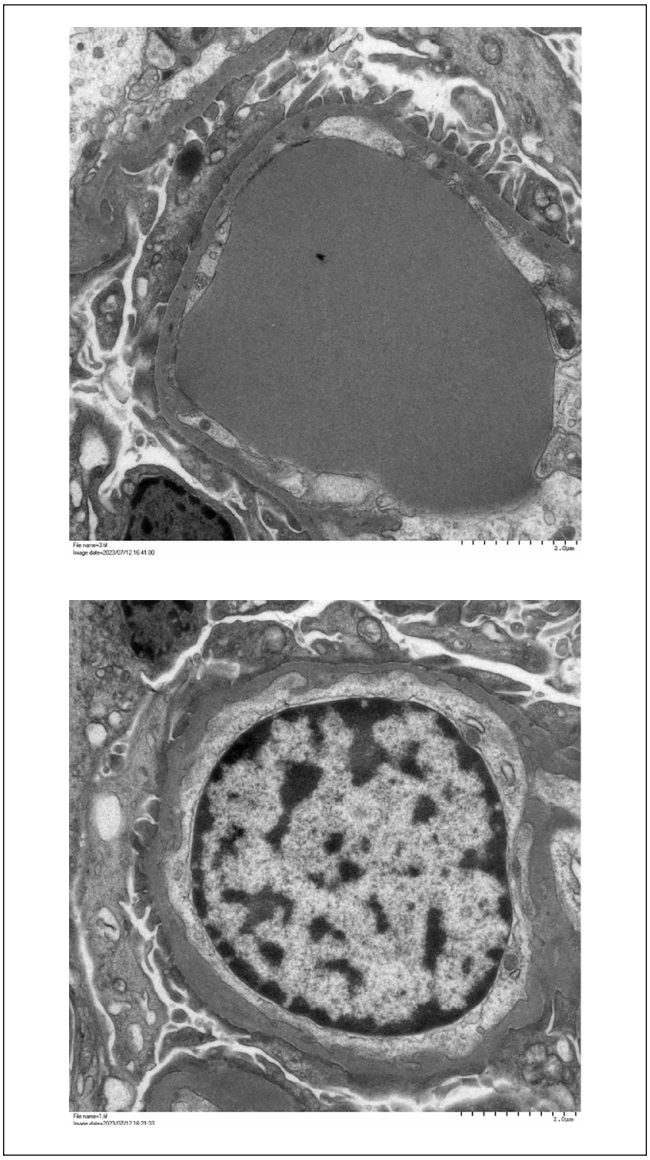

**Figure 2.** There were no deposits in the subepithelial and mesangial areas, although some loss of foot processes was observed. Endothelial cell swelling and subendothelial edema were observed.

to be a good explanation of proteinuria after renal crisis (glomerular ischemia) in this case. On the other hand, glomerular endothelial cells are also thought to have a barrier function for proteins.[6–8]

Moreover, several reports show that the risk of the systemic sclerosis renal crisis is associated with factors such as corticosteroid exposure, the presence of anti-RNA polymerase III antibodies, skin thickness, and significant tendon friction.[9] While this patient did not reveal specific antibodies, it is important to note that the positivity rate for these antibodies was different by sex, region, and age.[9] While this patient did not reveal specific antibodies, it is important to note that the positivity rate for these antibodies was different by sex, region, and age. Furthermore, there are additional risks associated with the renal crisis, including severe skin thickness and the use of steroid therapy. The patient was started on oral prednisone (30 mg/day) for skin sclerosis, there is a possibility that the dosage of 30 mg/day of steroid triggered the renal crisis. Therefore, it is crucial to be aware that using steroids at a dosage exceeding 10 mg/day carries a risk of a renal crisis. As a result, we must consider gradually reducing the steroid dosage and exploring alternative treatments for systemic sclerosis to prevent the recurrence of a renal crisis.

It is known that systemic sclerosis renal crisis causes endothelial damage and endothelial cell swelling.[1] However, it does not usually induce large amounts of proteinuria in renal crisis of systemic sclerosis. Additional unknown mechanisms between endothelial cells and podocyte injury would be affected in this case. Further studies are required to reveal the whole story of massive proteinuria in this condition.

This case showed nephrotic syndrome after the renal crisis of systemic sclerosis. In cases of systemic sclerosis, proteinuria and renal dysfunction are observed in approximately a quarter of patients.[10] The frequency of systemic sclerosis renal crisis is approximately 3%–5%,[11] but nephrotic syndrome is very rare in renal crisis cases. Around 75% of renal crises in systemic sclerosis occur in the first 4 years of the disease.[12] The onset of disease was standard in this case. This case is an uncommon manifestation of nephrotic syndrome post-renal crisis in systemic sclerosis. Notably, the patient experienced a renal crisis episode, but their systemic sclerosis-specific antibodies tested negative. One limitation of our study is the inability to establish a clear correlation between negative antibodies and renal kidney disease.

This case presents a rare occurrence of nephrotic syndrome following a renal crisis in systemic sclerosis. While proteinuria and renal dysfunction are observed in approximately a quarter of patients with systemic sclerosis, the development of nephrotic syndrome after a renal crisis is exceptionally uncommon.

## Conclusion

We report the first case of an unusual manifestation of nephrotic syndrome post-renal crisis in systemic sclerosis. It is necessary to observe the kidney biopsy when the broader understanding of renal complications associated with systemic sclerosis occur.

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### Author contributions

H.Y. and K.F. conceived the study. A.F., K.T., Y.K., and S.K. developed the theory and performed the experiments. S.K., K.N., and T.Y. advised the treatment therapy. N.H. and K.F. verified the pathological methods. K.F. encouraged A.F. to perform the experiments and supervised the findings. All authors discussed the results and contributed to the final article.

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## Ethics approval

Our institution does not require ethical approval for reporting individual cases or case series.

## Patient consent statement

Informed consent was obtained from all individual participants included in the study.
We especially had informed consent from patient in this case.

## Informed consent

Written informed consent was obtained from the patient(s) for their anonymized information to be published in this article.

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