Patterns of renal pathology in Chinese patients with systemic sclerosis undergoing renal biopsy at a tertiary medical center

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Abstract

Objective: We investigated renal injury characteristics in Chinese patients with systemic sclerosis (SSc) who had undergone renal biopsy.

Methods: We searched the medical records of patients with SSc who were hospitalized at Peking Union Medical College Hospital between January 1990 and August 2019. We analyzed the clinical characteristics and pathological results of these patients.

Results: We identified 25 patients who had undergone renal biopsy. Of these patients, 10 had scleroderma renal crisis (SRC); one underwent renal biopsy twice (for diffuse mesangial proliferative glomerulonephritis and for SRC); two had antineutrophil cytoplasmic antibody-associated glomerulonephritis; one had immunoglobulin M nephropathy; one had minimal change nephropathy; seven had lupus nephritis; one had scleroderma renal crisis with comorbid lupus nephritis; and two had drug-related kidney injury (caused by aristolochic acid in one and D-penicillamine in the other). Acute tubular necrosis was observed in the patient taking oral aristolochic acid, while minimal change nephropathy was observed in the patient with D-penicillamine-induced renal injury.

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Conclusions: SRC was the most commonly encountered renal damage in patients with SSc. We recommend biopsy for patients undergoing treatment for SRC who have persistent renal injury with proteinuria, regardless of hematuria. Rheumatologists in Eastern countries should be aware of aristolochic acid nephropathy.

Keywords
Systemic sclerosis, histopathology, renal biopsy, Chinese, lupus nephritis, scleroderma renal crisis, glomerulonephritis, aristolochic acid, penicillamine, proteinuria

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Introduction
Systemic sclerosis (SSc) is a type of chronic autoimmune disease that is characterized by fibrosis and vasculopathy. Approximately 60% to 70% of patients with SSc have renal injury. Prior studies in this area have focused on scleroderma renal crisis (SRC) because of its progressive pathology and life-threatening outcome. The use of captopril for treatment of SRC has significantly improved the prognosis of patients with SRC and many investigations have been performed regarding the diagnosis and management of SRC. Renal damage in SSc has also been reported to manifest as proteinuria, albuminuria, reduced renal filtration rate, autoantibody-related glomerulonephritis, and drug-related side effects; hence, renal biopsy constitutes an important examination for the diagnosis of SSc, as it may provide insight into the possible pathogenesis of SSc in affected patients. Because ethnicity-related differences have been reported in demographic features, autoantibody types, and clinical courses of patients with SSc, the present study investigated the kidney histopathology features of Chinese patients with SSc.

Patients and methods

Patient selection and diagnostic criteria
The ethics committee of Peking Union Medical College Hospital approved this study protocol (approval number: S-191). All included patients provided written informed consent. We did not have access to information that could identify individual participants, during or after data collection. We reviewed the data of patients with SSc who were hospitalized in our center from January 1990 to August 2019. We identified patients who had undergone renal biopsy and analyzed their clinical and laboratory data at baseline. Clinicians could encounter renal injury due to comorbid connective tissue disease in patients with SSc; therefore, patients with SSc who had comorbid connective tissue disease were also included in this investigation. All included patients met both the 1980 and 2013 American College of Rheumatology (ACR)/European League Against Rheumatism (EULAR) criteria for the classification of SSc. Of note, one patient initially met the criteria for SSc sine scleroderma. During follow-up, skin thickening of the fingers in both hands occurred, supporting a definite diagnosis of SSc. The definition of SRC in this study was based on the guidelines proposed by the United Kingdom Scleroderma Study Group. Patients were followed up by outpatient clinic visits or via telephone.

Review of renal biopsy sections
The interpretation of pathological renal biopsy was composed of three parts: light microscopy, immunofluorescence, and
electron microscopy. The operational details are provided in our previous publication; briefly, percutaneous renal biopsy was performed with ultrasound guidance. The pathological sections were reviewed by two independent pathologists who specialize in kidney diseases. If their findings were conflicting, the final pathological result was determined by discussion among a panel of pathologists.

Data analysis

All data analyses were performed using IBM SPSS Statistics for Windows, version 19.0 (IBM Corp., Armonk, NY, USA). Categorical variables are expressed as numbers and percentages. The normality of the data distribution for continuous variables was assessed using the Kolmogorov–Smirnov test. Variables for which distributions were not normal are presented as medians (ranges), whereas variables with normal distributions are presented as means ± standard deviations.

Results

Baseline characteristics of included patients

We reviewed the data of 1071 patients with SSC who were hospitalized in our center from January 1990 to August 2019. Of these 1071 patients, 25 had undergone renal biopsy and were included in this study. As shown in Table 1, 18 of the patients were women. The patients ranged in age from 14 years to 54 years (mean age, 37.8 years). The disease duration ranged from 0 years to 23 years (median disease duration, 4 years). The urine protein excretion within 24 hours varied from 0.3 g to 29.29 g. The median estimated glomerular filtration rate of all patients was 27.60 mL/(min·1.73 m²) (interquartile range, 13.52–93.42 mL/(min·1.73 m²)). Fundus lesions related to hypertension occurred in six patients. The gastrointestinal system was involved in 17 patients. Antinuclear antibodies were present and anticientromere antibodies were absent in all patients, based on serum immunological examinations. Renal damage due to antineutrophil cytoplasmic antibody (ANCA)–associated vasculitis was observed in two patients; further laboratory tests revealed the presence of myeloperoxidase–ANCA in these two patients. The clinical features of patients with SSC who had SRC are summarized in Tables 2 and 3. There were three men and eight women with SRC; their median duration of disease was 1 year.

Table 1. Demographic and clinical characteristics of 25 Chinese patients with systemic sclerosis who underwent renal biopsy during the study period.

| Characteristic                        | n (%)  |
|--------------------------------------|--------|
| Sex (female)                         | 18 (72.0) |
| Diffuse cutaneous scleroderma        | 11 (44.0) |
| Limited cutaneous scleroderma        | 4 (16.0)  |
| SSC sine scleroderma                 | 1 (4.0)   |
| SSC overlap syndrome                 | 9 (36.0)  |
| Disease duration (years)             | 4       |
| Raynaud’s phenomenon                 | 18 (72.0) |
| Fingertip ulcer                      | 7 (28.0)  |
| Arthritis                            | 7 (28.0)  |
| Gastrointestinal involvement         | 17 (68.0) |
| Interstitial lung disease            | 16 (64.0) |
| Cardiac involvement                  | 19 (76.0) |
| Antinuclear antibody (+)             | 25 (100.0) |
| Anti-Scl-70 antibody (+)              | 9 (36.0)   |
| Anti-centromere antibody (+)         | 0 (0.0)    |
| Anti-SSA antibody (+)                | 6 (24.0)   |
| P-ANCAa                              | 2 (8.0)    |
| MPO-ANCAb                            | 2 (8.0)    |
| Elevated erythrocyte sedation rate   | 16 (64.0)  |

aDetected by indirect immunofluorescence.
bExamined by enzyme-linked immunosorbent assay.

Abbreviations: SSC, systemic sclerosis; P-ANCA, perinuclear anti-neutrophil cytoplasmic antibodies; MPO-ANCA, myeloperoxidase antineutrophil cytoplasmic antibodies.
Manifestations of renal pathology

Multiple patterns of renal pathology were found in this study, including SSc-related renal injury (n = 16; Table 4), lupus nephritis (LN; n = 7), and drug-associated renal impairment (n = 2; caused by *Aristolochiae fructus* in one patient and penicillamine in the other). Notably, percutaneous renal biopsy was performed twice in three patients (Table 5); among these three patients, two exhibited LN twice. Changes in the pathologic type of LN were observed in these two patients. The renal pathological patterns of the remaining 22 patients are demonstrated in Table 6. Importantly, thrombotic microangiopathy was observed in all patients with SRC. An “onion skin” appearance was present, in combination

| Clinical manifestation                                      | n (%) |
|-------------------------------------------------------------|-------|
| Diffuse cutaneous scleroderma                                | 7 (63.6) |
| Limited cutaneous scleroderma                                | 3 (27.3) |
| Systemic sclerosis overlap syndrome                          | 1 (9.09) |
| Raynaud’s phenomenon                                         | 5 (45.5) |
| Hypertensive retinopathy                                     | 5 (45.5) |
| Oliguria                                                     | 4 (36.4) |
| Nocturia                                                     | 2 (18.2) |
| Interstitial lung disease                                    | 6 (54.5) |
| Pleural effusion                                             | 3 (27.3) |
| Gastrointestinal involvement                                 | 6 (54.5) |
| Cardiac involvement                                          | 9 (81.8) |

**Table 2.** Summary of the clinical characteristics of 11 Chinese patients with systemic scleroderma who had scleroderma renal crisis.

| Patient No. | Sex | Disease course (months) | Blood pressure (mmHg) | Serum Cr (μmol/L) | Abnormal fundus | 24-hour urinary protein (g) | Hg (g/L) | Anti-scl-70 antibody |
|-------------|-----|-------------------------|-----------------------|-------------------|----------------|----------------------------|----------|---------------------|
| 1           | F   | 48                      | 220/110               | 998.9             | +              | 0.65                       | 104      | +                   |
| 2           | F   | 10                      | 190/130               | 651.5             | +              | 0.87                       | 82       | +                   |
| 3           | M   | 12                      | 180/130               | 1664.5           | –              | 1.5                        | 96       | +                   |
| 4           | F   | 1                       | 230/110               | 195               | +              | 0.3                        | 116      | –                   |
| 5           | F   | 60                      | 190/120               | 259               | +              | 4.53                       | 82       | –                   |
| 6           | F   | 8                       | 220/120               | 715               | –              | 1.9                        | 96       | +                   |
| 7           | F   | 228                     | 200/130               | 294               | –              | 3.67                       | 96       | –                   |
| 8           | F   | 48                      | 170/110               | 254               | –              | 1                          | 116      | –                   |
| 9           | M   | 4                       | 190/110               | 420               | –              | 1.67                       | 67       | +                   |
| 10          | M   | 5                       | 170/100               | 626               | –              | 0.9                        | 120      | –                   |
| 11          | F   | 19                      | 160/110               | 273               | –              | 0.95                       | 129      | –                   |

*Patient underwent renal biopsy twice; diffuse mesangial proliferative glomerulonephritis was observed in the first renal biopsy and scleroderma renal crisis was revealed in the following renal biopsy.*

**Table 4.** Clinical diagnosis of renal impairment in 16 Chinese patients with systemic scleroderma who exhibited renal damage caused by scleroderma.

| Clinical diagnosis of renal impairment | n (%) |
|---------------------------------------|-------|
| SRC                                   | 9 (56.3) |
| SRC + lupus nephritis                 | 1 (6.3) |
| ANCA-related glomerulonephritis       | 2 (12.5) |
| Diffuse MesPGN + SRC                  | 1* (6.3) |
| Other                                 | 3 (18.8) |

Abbreviations: Cr, creatine; Hg, hemoglobin; F, female; M, male.
with luminal stenosis, endothelial edema and proliferation, intimal mucoid change and edema, erythrocyte fragments within the arterial vessel wall, interlobular artery fibrinoid necrosis, ischemic glomeruli, hyalinosis in small arteries, and thrombi. The proliferation of arteriole elastic fibers, which exhibited an “onion skin” concentric appearance with luminal stenosis, was the most common manifestation in patients with SRC.

Among three patients with SSc, the following pathological findings were observed: mesangial proliferative glomerulonephritis in one patient, immunoglobulin M nephropathy in one patient, and minimal change nephropathy in one patient. In the patient who had mesangial proliferative glomerulonephritis, deposition of IgG in the glomerular basement membrane and deposition of fine-particle immune complexes in the tubular basement membrane were detected by immunofluorescence. Depositions of IgA, IgM, C3, C4, Clq, hepatitis B surface antigen, and fibrin were not detected in the patient. The patient was also negative for serum hepatitis B surface antigen. The renal pathology of two patients with drug-associated renal impairment included A. fructus-related acute tubular necrosis in one patient and penicillamine-related minimal change nephropathy in the other patient. Light microscope analysis revealed that the patient with A. fructus-related renal lesions also exhibited mesangial proliferative glomerulonephritis accompanied by focal sclerosis.

| Table 5. Consecutive renal biopsy findings of three Chinese patients with systemic sclerosis who underwent percutaneous renal biopsy twice. |
|-----------------|-------------------------------------------------|
| Patient No.     | First renal pathology                           | Second renal pathology                      |
| 1               | Diffuse mesangial proliferative glomerulonephritis | Scleroderma renal crisis and malignant hypertension |
| 2               | IV lupus nephritis                              | IV and V lupus nephritis                     |
| 3               | V lupus nephritis                               | III and V lupus nephritis                    |

| Table 6. Kidney pathology in the remaining 22 Chinese patients with systemic sclerosis who did not undergo percutaneous renal biopsy twice. |
|-------------------------------------------------|-----------------|-------------------------------------------------|
| Kidney pathology                               | n (%)           |
| Scleroderma renal crisis                        | 9 (40.9)        |
| Scleroderma renal crisis and III lupus nephritis| 1 (4.5)         |
| III Lupus nephritis                             | 1 (4.5)         |
| IV Lupus nephritis                              | 2 (9.1)         |
| V Lupus nephritis                               | 1 (4.5)         |
| IV + V Lupus nephritis                          | 1 (4.5)         |
| Acute tubular necrosis complicated with mesangial proliferative glomerulonephritis (aristolochic acid nephropathy) | 1 (4.5)         |
| Drug-associated minimal change nephropathy      | 1 (4.5)         |
| Minimal change nephropathy                      | 1 (4.5)         |
| Pauci-immune crescentic glomerulonephritis      | 2 (9.1)         |
| Mesangial proliferative glomerulonephritis      | 1 (4.5)         |
| IgM nephropathy                                 | 1 (4.5)         |

**Treatment and outcome**

Angiotensin-converting enzyme inhibitors (ACEIs) were preferentially used to control the blood pressure of 11 patients with SRC, including the patient with concurrent SRC and LN. The ACEI full dose was equivalent to 200 mg of captopril per day. If blood pressure was not managed well, other antihypertensive drugs were added (e.g., angiotensin receptor blockers, calcium channel blockers, or beta blockers). Two of the 11 patients were lost to follow-up. For the
remaining nine patients, renal function was recovered in two; four were stable and did not require dialysis. Finally, two patients died and one patient underwent regular dialysis.

The two patients with ANCA-related glomerulonephritis received large doses of glucocorticoids (GCs) and cyclophosphamide. During follow-up, one patient exhibited mildly elevated serum creatinine, while the other patient underwent dialysis. Among the three patients who had diffuse mesangial proliferative glomerulonephritis, immunoglobulin M nephropathy, or minimal change nephropathy (each had a different disease), all were treated with GCs and immunosuppressants (cyclophosphamide and methotrexate). The adjuvant drugs included ACEIs and angiotensin receptor blockers. The patients’ conditions improved after treatment. The seven patients with LN were administered large doses of GCs and immunosuppressive agents (i.e., cyclophosphamide, mycophenolate mofetil, leflunomide, or cyclosporin A). One patient underwent dialysis and the remaining six patients were stable.

*A. fructus* treatment led to drug-related renal damage in one patient; this patient began dialysis and stopped taking *A. fructus* at the onset of renal damage. The patient was also treated with GCs, ACEIs, and angiotensin receptor blockers. After 14 years of follow-up, the patient discontinued dialysis and had a serum creatinine level of 170 μmol/L. D-penicillamine treatment led to drug-related renal damage in one patient; this patient stopped taking D-penicillamine shortly after the renal damage was observed. After treatment with GCs, cyclophosphamide, and ACEIs, this patient recovered normal renal function.

**Discussion**

The main types of kidney involvement in patients with SSc are SRC, chronic kidney disease, and inflammatory kidney damage. A recently published study demonstrated that SRC, nephrosclerosis, and tubulointerstitial nephritis were the primary renal pathological changes in Japanese patients with SSc. Other acute renal complications may also occur, especially in patients with SSc and comorbid SLE. The present study constituted a preliminary investigation of the pathological characteristics of Chinese patients with SSc who had undergone renal biopsy.

The recognition of SRC has improved over time. It is most likely to occur in women and in patients with rapidly progressive diffuse cutaneous SSc, within the first 3 to 5 years from disease onset. Elevated blood pressure and serum creatinine increased the risk of death in patients with SRC. In the present study, all 11 patients with SRC had elevated blood pressure and serum creatinine at baseline; in most patients, blood pressure could be controlled to normal with ACEIs, while other patients required treatment with additional antihypertensive drugs in some patients. Two patients had died by the end of the follow-up period. Renal function recovered to varying degrees in six of the 11 patients.

An underlying cause of acute renal failure in some patients with SSc is ANCA-associated glomerulonephritis, which can lead to rapidly progressive glomerulonephritis. The incidence of ANCA-related vasculitis in patients with SSc is low. Additionally, 77% to 83% of patients with SSc exhibit acute renal insufficiency with normal or slightly elevated blood pressure. These patients exhibit proteinuria, which may indicate the onset of nephrotic syndrome; they may also exhibit active urinary sediment. Microangiopathic hemolytic anemia has not been observed in patients with SSc who had ANCA-associated glomerulonephritis. In the present study, two patients exhibited ANCA-associated glomerulonephritis, which manifested as
rapidly progressive glomerulonephritis. Both patients demonstrated anti-myeloperoxidase antibodies. D-penicillamine has been reported to induce ANCA-related vasculitis in patients with Wilson’s disease. However, the two patients with ANCA-associated glomerulonephritis denied prior treatment with D-penicillamine. In this study, we found that one patient had been diagnosed with SSc sine scleroderma; Raynaud’s phenomenon had been present for 5 years. Laboratory examination showed positive anti-Scl-70 antibody. In addition, renal damage, pulmonary interstitial fibrosis, esophageal dilation, and intestinal malabsorption were present. The treatment for these two patients with ANCA-associated glomerulonephritis differed from the treatment for patients with SRC. High doses of GCs, cyclophosphamide, and rituximab could induce and maintain remission in most patients with ANCA-associated glomerulonephritis; moreover, renal pathology could provide valuable information to guide the differential diagnosis.

Salomon et al. reported that minor and nonspecific renal changes were ubiquitous in patients with scleroderma, even in subclinical forms. Mesangial proliferative glomerulonephritis, immunoglobulin M nephropathy, and minimal change nephropathy were present in our patients. Membranous glomerulonephritis has been reported in patients with SSc, but this type of renal damage was not present in our patients. Interestingly, we identified a patient who had LN and comorbid SRC. A prior report also described a patient with SSc and comorbid SLE, in whom LN was observed at the early stage of disease, followed by the occurrence of SRC. The precipitating factor was the usage of high-dose corticosteroid treatment for LN, which was consistent with the clinical history of the patient in our study. Furthermore, changes in the pathologic type of LN were observed in two patients. In clinical practice, physicians should be cautious when differentiating between SRC and an LN flare. Early intervention is critical in patients with SRC. In our study, patients with SSc who had delayed confirmation of renal crisis were found to present with significantly greater impairment of renal function, compared with patients with SSc who had an different renal pathology (e.g., LN). Therefore, rapid ACEI initiation and control of hypertension are essential in patients with SSc who present with severe acute kidney injury.

Aristolochic acid caused acute tubular necrosis in one patient in this study, while D-penicillamine caused minimal change nephropathy in another patient. Aristolochic acid nephropathy was first recognized in the early 1990s. The pattern of aristolochic acid nephropathy kidney injury in our patient was consistent with that reported in previous literature. Renal damage caused by D-penicillamine in patients with SSc has been previously reported; it can manifest as Goodpasture-like syndrome or proteinuria. In our study, D-penicillamine-related renal damage manifested as nephrotic syndrome. Minimal change nephropathy was confirmed by renal biopsy. Our findings suggest that D-penicillamine- and aristolochic acid-related renal injuries are not rare in patients with SSc. Rheumatologists in Eastern countries should be aware of these disease entities, especially in patients from rural areas who have a history of taking traditional Chinese medicine. Our findings demonstrated that treatment with GCs and/or immunosuppressants might be suitable for patients with SSc who have D-penicillamine- or aristolochic acid-related renal damage.

The primary limitation of this study was its small sample size. A large-scale study regarding the pathological features of SSc in kidney biopsy is warranted to confirm our conclusions. Because renal biopsy was typically performed when patients had an
unclear initial diagnosis, the findings in our study may not reflect the overall renal involvement in patients with SSc.

In conclusion, we observed various types of renal lesions in patients with SSc. SRC was the most prevalent manifestation. LN, ANCA-associated glomerulonephritis, aristolochic acid-induced renal lesions, and D-penicillamine-induced renal lesions were also present in these patients; these types of injuries can cause symptoms similar to those of SRC. Distinguishing between SRC and the other types of lesions is critical because of the distinct management approaches. Our findings suggest that, if an etiological diagnosis of SSc renal damage is uncertain, renal biopsy should be performed to confirm the diagnosis and exclude other potential causes. Additionally, we recommend biopsy for patients undergoing treatment for SRC who have persistent renal injury with proteinuria, regardless of hematuria.

Declaration of conflicting interest
The authors declare that there is no conflict of interest.

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References
1. Lusco MA, Najafian B, Alpers CE, et al. AJKD atlas of renal pathology: systemic sclerosis. *Am J Kidney Dis* 2016; 67: e19–e20.
2. Steen VD, Costantino JP, Shapiro AP, et al. Outcome of renal crisis in systemic sclerosis: relation to availability of angiotensin converting enzyme (ace) inhibitors. *Ann Intern Med* 1990; 113: 352–357.
3. Lynch BM, Stern EP, Ong V, et al. UK scleroderma study group (UKSSG) guidelines on the diagnosis and management of scleroderma renal crisis. *Clin Exp Rheumatol* 2016; 34: 106–109.
4. Ghossein C, Varga J and Fenves AZ. Recent developments in the classification, evaluation, pathophysiology, and management of scleroderma renal crisis. *Curr Rheumatol Rep* 2016; 18: 5.
5. Woodworth TG, Suliman YA, Li W, et al. Scleroderma renal crisis and renal involvement in systemic sclerosis. *Nat Rev Nephrol* 2016; 12: 678–691.
6. Bruni C, Cuomo G, Rossi FW, et al. Kidney involvement in systemic sclerosis: from pathogenesis to treatment. *J Scleroderma Relat Disord* 2018; 3: 43–52.
7. Steen V, Domsie RT, Lucas M, et al. A clinical and serologic comparison of African American and Caucasian patients with systemic sclerosis. *Arthritis Rheum* 2012; 64: 2986–2994.
8. Nandiwada SL, Peterson LK, Mayes MD, et al. Ethnic differences in autoantibody diversity and hierarchy: more clues from a us cohort of patients with systemic sclerosis. *J Rheumatol* 2016; 43: 1816–1824.
9. Subcommittee for Scleroderma Criteria of the American Rheumatism Association Diagnostic and Therapeutic Criteria Committee. Preliminary criteria for the classification of systemic sclerosis (scleroderma). *Arthritis Rheum* 1980; 23: 581–590.
10. van den Hoogen F, Khanna D, Fransen J, et al. 2013 classification criteria for systemic sclerosis: an American College of Rheumatology/European League against Rheumatism collaborative initiative. *Arthritis Rheum* 2013; 65: 2737–2747.
11. Poormoghim H, Lucas M, Fertig N, et al. Systemic sclerosis sine scleroderma: demographic, clinical, and serologic features and survival in forty-eight patients. *Arthritis Rheum* 2000; 43: 444–451.
12. Wang Z, Li M, Zeng X, et al. Hepatitis B virus-associated antigen deposition in renal tissue from patients with systemic lupus erythematosus. *J Rheumatol* 2012; 39: 974–978.
13. Donohoe JF. Scleroderma and the kidney. *Kidney Int* 1992; 41: 462–477.

14. Ichikawa K, Konta T, Sato H, et al. The clinical and pathological characteristics of nephropathies in connective tissue diseases in the Japan renal biopsy registry (J-RBR). *Clin Exp Nephrol* 2017; 21: 1024–1029.

15. Penn H, Howie AJ, Kingdon EJ, et al. Scleroderma renal crisis: patient characteristics and long-term outcomes. *QJM* 2007; 100: 485–494.

16. DeMarco PJ, Weisman MH, Seibold JR, et al. Predictors and outcomes of scleroderma renal crisis: the high-dose versus low-dose D-penicillamine in early diffuse systemic sclerosis trial. *Arthritis Rheum* 2002; 46: 2983–2989.

17. Scussel-Lonzetti L, Joyal F, Raynauld JP, et al. Predicting mortality in systemic sclerosis: analysis of a cohort of 309 French Canadian patients with emphasis on features at diagnosis as predictive factors for survival. *Medicine (Baltimore)* 2002; 81: 154–167.

18. Teixeira L, Mouthon L, Mahr A, et al. Mortality and risk factors of scleroderma renal crisis: a French retrospective study of 50 patients. *Ann Rheum Dis* 2008; 67: 110–116.

19. Chan PT and Mok CC. Pauci-immune crescentic glomerulonephritis in limited cutaneous systemic sclerosis. *Clin Rheumatol* 2012; 31: 1273–1277.

20. Rho YH, Choi SJ, Lee YH, et al. Scleroderma associated with ANCA-associated vasculitis. *Rheumatol Int* 2006; 26: 369–375.

21. Bienaime F, Clerbaux G, Plaisier E, et al. D-penicillamine-induced ANCA-associated crescentic glomerulonephritis in Wilson disease. *Am J Kidney Dis* 2007; 50: 821–825.

22. Lee Y, Lee ST and Cho H. D-penicillamine-induced ANA(+) ANCA(+) vasculitis in pediatric patients with Wilson’s disease. *Clin Nephrol* 2016; 85: 296–300.

23. Furuta S and Jayne D. Emerging therapies in antineutrophil cytoplasm antibody-associated vasculitis. *Curr Opin Rheumatol* 2014; 26: 1–6.

24. Gomez-Puerta JA, Quintana LF, Stone JH, et al. B-cell depleting agents for ANCA vasculitides: a new therapeutic approach. *Autoimmun Rev* 2012; 11: 646–652.

25. Salomon MI, Lamovec J and Tchertkoff V. Renal lesions in scleroderma. *Angiology* 1978; 29: 569–578.

26. Wielosz E, Majdan M, Suszek D, et al. Nephrotic syndrome as a clinical manifestation of systemic sclerosis. *Rheumatol Int* 2007; 27: 1087–1089.

27. Alayoud A, Qamouss O, Hamzi A, et al. Scleroderma renal crisis precipitated by steroid treatment in systemic lupus erythematosus and scleroderma overlap syndrome. *Arab J Nephrol Transplant* 2012; 5: 153–157.

28. Luciano RL and Perazella MA. Aristolochic acid nephropathy: epidemiology, clinical presentation, and treatment. *Drug Saf* 2015; 38: 55–64.

29. Derk CT and Jimenez SA. Goodpasture-like syndrome induced by D-penicillamine in a patient with systemic sclerosis: report and review of the literature. *J Rheumatol* 2003; 30: 1616–1620.

30. Steen VD, Syzd A, Johnson JP, et al. Kidney disease other than renal crisis in patients with diffuse scleroderma. *J Rheumatol* 2005; 32: 649–655.