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Renal sarcoidosis: renal pathology guides diagnosis and prognosis

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Abstract

Background While many studies have reported renal involvement in sarcoidosis, there is limited description of the pathological manifestations of renal sarcoidosis (RS). This study aimed to explore the standardized pathological diagnosis of RS while evaluating the relationship among pathology, clinical manifestations, and prognosis.

Methods We conducted a retrospective, single-center study of RS in renal biopsy cases treated in our department between January 2019 and December 2023.

Results We identified 5 patients (4 men, 1 woman; median age 52 years, IQR 36–61 years). Two patients were diagnosed with non-caseating granulomatous interstitial nephritis (GTN), while two patients were diagnosed with tubulointerstitial nephritis without granulomas (TIN), and one patient was diagnosed with acute tubular necrosis (ATN). The grading of tubulointerstitial acute inflammation revealed 2 cases (case 4 and case 5) graded as (+++), with serum creatinine levels greater than 900 μmol/L at onset. Additionally, there were 2 cases (case 2 and case 3) gradedas (+), and 1 case (case 1)graded as (-), with serum creatinine levels approximately 400 μmol/L at onset. All 5 cases exhibited an interstitial fibrosis grade of (-). However, in the second renal biopsy following recurrence in case 4, the interstitial fibrosis grade increased to (++). In two patients with GTN, immunohistochemical staining revealed that the infiltrating lymphocytes were predominantly CD4 + T cells, which formed nodular granulomas and were surrounded by CD8 + T cells. A favorable response to steroid therapy was noted in all cases, especially in case 1, 2, and 3.

Conclusions The pathological manifestations of RS primarily consist of acute TIN with or without granuloma formation. Quantifying the pathological grade may assist in guiding treatment decisions and predicting prognosis.

Keywords Sarcoidosis, Renal sarcoidosis, Acute kidney disease, Pathology, Outcome

Introduction

Sarcoidosis is a systemic inflammatory disease that can affect multiple organs. It is characterized by an increased cellular immune response to an unknown antigen, resulting in the accumulation of lymphocytes and other mononuclear cells in non-caseating epithelioid granulomas [1, 2]. While the lungs and lymph nodes are the most commonly affected sites (75–90%), other organs such as the eyes, bone marrow, kidneys, liver and spleen can also be affected [3].

The prevalence of renal sarcoidosis (RS) in the world is not known exactly, but case studies report a range of 0.3–3.5% [4]. Sarcoidosis can cause various types of glomerulonephritis, such as focal and segmental glomerulosclerosis mesangial proliferative glomerulonephritis, IgA nephropathy, membranoproliferative and crescentic glomerulonephritis [5]. However, the two most common findings are granulomatous interstitial nephritis

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(GIN) and stone disease or nephrocalcinosis secondary to hypercalcemia [6–9]. Although kidney biopsy is considered the gold standard for diagnosis and prediction of outcome in RS, especially in the absence of other extrarenal signs [10], it is not commonly performed due to the frailty of many patients, the severe increase in serum creatinine or the high risk of complications associated with the technique. So, few studies have investigated the specific pathological manifestations of RS.

There is currently a lack of relevant studies addressing the types of infiltrating cells in renal interstitial granulomas, the severity of inflammatory infiltration, and the chronicity of the lesions in RS. This study aims to address these limitations by examining a cohort of patients with biopsy-confirmed RS in a single center to explore (a) the pathological manifestations of RS, (b) the standard description of pathology in RS, and (c)the relationship between clinicopathological characteristics and outcomes of these patients.

Methods

Patients

We conducted a retrospective single-center study of patients diagnosed with RS in our Department of Nephrology between Jan 2019 and Dec 2023. Patients meet the following inclusion criteria: (1) confirmed sarcoidosis according to the statement of the Official American Thoracic Society [2]; (2) renal histology compatible with the diagnosis of RS (interstitial nephritis with or without granuloma, and renal calcinosis); and (3) exclusion of any alternative diagnosis. All data were collected by 1 author, and were systematically reviewed by the same person and another author.

Clinical and laboratory data at presentation

For all cases, age, sex, history, medical examination, affected organs and laboratory tests were compiled. The laboratory workup included serum creatinine level (μmol/L), estimated glomerular filtration rate (eGFR), serum kalium, results of urine sediment examination and 24-h urine protein levels, etc. Hypercalcemia was defined as total plasma calcium > 2.75 mmol/L. Specific treatment of RS (steroid and/or immunosuppressive treatment) was recorded for all patients. Patients were followed up in the outpatient clinic or by telephone.

Renal pathology

Renal biopsy specimens were examined in our Laboratory of Renal Pathology. All kidney biopsy samples were processed for light microscopy (LM), immunofluorescence (IF) and electronic microscopy (EM) examination. The interstitial inflammation was graded as the extent of inflammatory cells in the cortex: 0 = no or trivial interstitial inflammation (< 10% of unscarred parenchyma), + = 10–25% of parenchyma inflamed, 2 + = 26–50% of parenchyma inflamed, 3 + = more than 50% of parenchyma inflamed. Interstitial fibrosis with tubular atrophy is evaluated according to the extent of interstitial fibrosis with tubular atrophy in the cortex: 0 = no or trivial interstitial fibrosis (< 5% of unscarred parenchyma), 1 + = 6–25% of interstitial fibrosis, 2 + = 26–50% of interstitial fibrosis, 3 + = more than 50% of interstitial fibrosis. Immunohistochemical (IHC) staining (CD3, CD4, CD8, CD20, and CD38) were performed to identify cell components. All of the specimens were reviewed by three observers in our center.

This research was in compliance with the Declaration of Helsinki, and approved by the Ethics Committee of Peking University People's Hospital (2023PHB190-001). Informed consent was obtained from all participants.

Statistical analysis

Statistical analysis was performed with SPSS version 24.0 statistical software package (SPSS, Chicago, IL). Continuous data were expressed as means with standard deviations (SDs) or as medians with interquartile ranges (IQRs). Categorical data were presented as proportions. Mann-Whitney U and paired t-tests were used to compare month 0 with month 1 serum creatine. $P < 0.05$ was considered to denote statistical significance.

Results

Clinical and laboratory data of patients

Five patients were retrospectively identified. The demographic, clinical manifestations and laboratory characteristics are summarized in Table 1. The median age of the patients at kidney biopsy was 52 years old (IQR 36–61), and the median duration from initial onset symptoms to renal biopsy was 2 months (IQR 2–11). At the time of renal biopsy, all patients had severely impaired renal function, with a median serum creatinine of 456 μmol/L (IQR 430.5–942.5). The mean proteinuria level at the onset of renal involvement was estimated to be 0.5 g/d (IQR 0.2–0.73). No patients had microscopic hematuria, hypouricemia, hypophosphatemia, or glucosuria. Acute kidney injury (AKI) was the primary reason for the renal biopsy in these cases.

Pathology features

Out of the total patients, two (40%) patients were diagnosed with non-caseating GTIN. Another two (40%) patients were diagnosed with TIN without granuloma, and renal calcinosis simultaneously. The remaining patient (20%) was diagnosed with acute tubular necrosis (ATN) and renal calcinosis. A detailed summary of the pathological findings in these patients are listed in Table 2.

Table 1 Demographics and clinical characteristics

	case 1	case 2	case 3	case 4	case 5
Age (years)	31	52	41	61	61
Gender	M	M	M	F	M
Combined diseases	-	HBP、DM	gout	-	-
Time from initial symptom to kidney biopsy (months)	2	2	2	10	12
initial symptom	bone pain	fatigue	bone pain and fever	fatigue	anorexia
Extra-renal manifestations	lung and lymph nodes	lung and lymph nodes	lung and lymph nodes	lung and lymph nodes	lung and lymph nodes
Hypercalcemia	Y	Y	Y	N	N
PTH (pg/mL)	6.6	NA	8.09	6.26	3.27
Creatinine (μmol/L)	449	412	415	902	983
eGFR (mL/min per 1.73m^2)	23	18.3	20.5	5.4	6.19
Hypercalciuria	Y	Y	Y	N	N
24-h urine protein (g/24 h)	0.5	0.8	0.66	0.18	0.23
Cause of renal biopsy	AKI	AKI	AKI	AKI	AKI

eGFR=estimated glomerular filtration rate; PTH=parathyroid hormone; AKI=acute kidney injury; NA=not applicable; N=no; Y=yes. HBP=high blood pressure; DM=diabetes mellitus

Table 2 Pathologic findings in patients

	Case 1	Case 2	Case 3	Case 4	Case 5
Tubulointerstitium diagnosis	ATN	TIN	TIN	GTIN	GTIN
Acute lesion					
Renal tubules					
Calcinosis	Y	Y	Y	N	N
Loss of brush border	Y	Y	Y	Y	Y
Renal interstitium					
Granulomatous lesions	-	-	-	multiple	multiple
Inflammation cells	Lymphocytes, Monocytes	Lymphocytes, Monocytes, eosinophils	Lymphocytes, Monocytes	Lymphocytes, Monocytes	Lymphocytes, Monocytes, eosinophils
Grade of interstitium infiltrate	-	+	+	+++	+++
Chronic lesion					
Tubular atrophy	Y	Y	Y	Y	Y
Grade of interstitial fibrosis	-	-	-	First RB: - Second RB: ++	-
Glomerular disease	-	DN (Class I)	-	-	-
Ischemic sclerosis	-	-	1/9	First RB: 2/14 Second RB:0/9	2/6

ATN=acute tubular necrosis; TIN=tubulointerstitial nephritis; GTIN=granulomatous tubulointerstitial nephritis; Y=yes; N=no. DN=Diabetic Nephropathy

Four patients (cases 2, 3, 4 and 5) showed evidence of an acute interstitial inflammation on renal biopsy histology. The light microscopy revealed diffuse interstitial inflammation consisting of numerous lymphocytes and epithelioid cells or multinucleated giant cells associated with non-caseating granulomas, and few eosinophils (Fig. 1A and B). There was no infiltration of neutrophilic granulocytes in the kidney biopsy specimens. Acid-fast staining was negative in all patients. In Cases 4 and 5, LM revealed the formation of multiple granulomas within the renal interstitium. The acute inflammation in the renal interstitium was graded as 3+, while the chronic fibrosis was graded as (-) (Fig. 1A). IHC staining was performed in these two cases who were diagnosed with GTN and showed predominant infiltration of CD4+T cells, which formed nodular granulomas surrounded by CD8+T cells (Fig. 2A and B). Additionally, small units of infiltrative CD20+B cells were detected in the interstitium. CD38+and CD138+cells were extremely rare.

In contrast, the pathological findings of cases 2 and 3 were primarily characterized by acute TIN without granulomas, with acute renal interstitial inflammation graded as (+)and chronic fibrosis also graded as (-) (Fig. 1B). The pathological findings of case 1 predominantly indicated

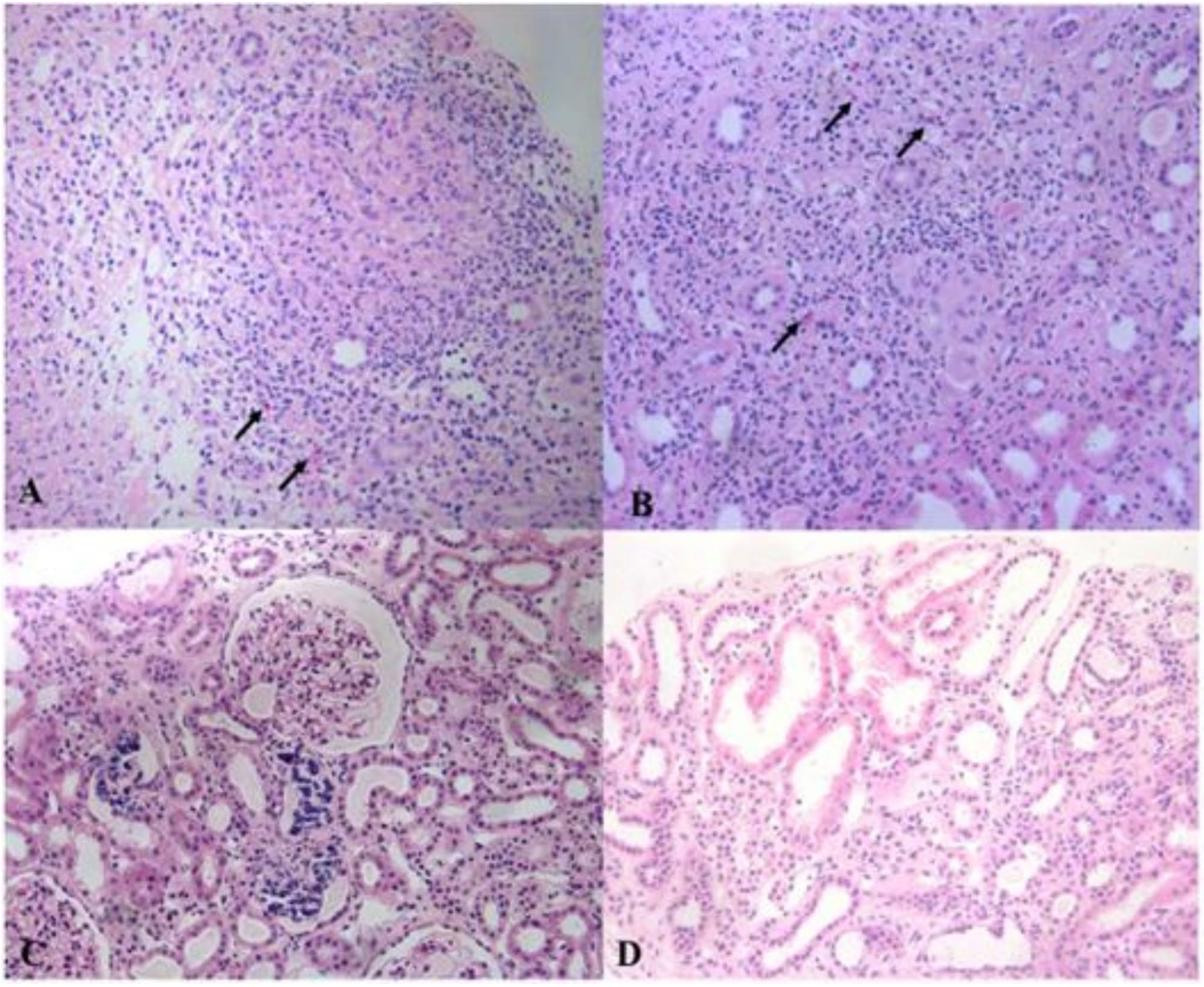

Fig. 1 Renal interstitial lesions detected by light microscopy. Interstitial nephritis characterized by a significant presence of lymphocytes in the renal interstitium, along with epithelioid cells and few eosinophils (arrows). (**A**) Non-caseating granulomatous interstitial nephritis (case4, HE; ×100). (**B**) Interstitia nephritis without granulomas(case 2, HE; ×100). (**C**) Extensive presence of calcium deposits is observable within the lumen of the renal tubules. (case 1, HE; ×100). (**D**) Loss of brush border, tubular dilatation, cytoplasmic vacuolization, and prominent nucleoli are also observed

ATN attributed to tubular lumen calcinosis, with no significant inflammatory infiltration or fibrosis observed in the renal interstitium. Consequently, both acute inflammation and chronic fibrosis grades of the renal interstitium were recorded as (-) (Fig. 1C).

All patients exhibit signs of tubulitis and tubular degeneration, including loss of brush border, tubular dilatation, cytoplasmic vacuolization, and prominent nucleoli (Fig. 1D).

Treatment and outcome

These five patients were treated with oral prednisone at different doses ranging from 0.8 to 1 mg/Kg/day. After one month of treatment, there was a significant improvement in renal function. The treatment and outcomes of the patients are summarized in Table 3.

Recurrence was observed in a single patient, specifically Case 4, who had initially been treated with oral prednisone. The second kidney biopsy revealed GTIN and more severe interstitial fibrosis compared to the first biopsy (Table 2). These findings were interpreted as being most consistent with recurrent RS. After increasing the dose of glucocorticoids and combining with azathioprine, we observed a subsequent decrease in serum creatinine levels, and we are continuing to follow up.

Discussion

This study demonstrates that the typical pathological presentations of RS were acute TIN (with or without granulomas) and nephrocalcinosis. The infiltrating lymphocytes were CD4+T cells forming nodular granulomas surrounded by CD8+T cells. The graded description of

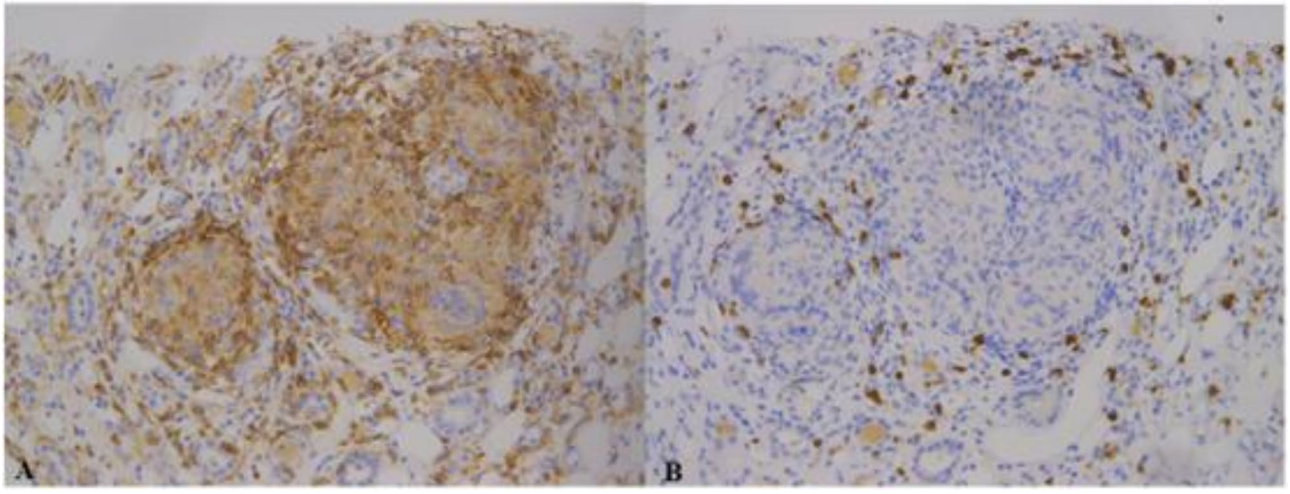

Fig. 2 IHC findings. (**A**) CD4 + lymphocytes are located in the center of nodular granulomas (case4, CD4; ×100). (**B**) CD8 + lymphocytes are located in the periphery of nodular granulomas (case4, CD8; ×100)

Table 3 Follow up summary for patients

	Case 1	Case 2	Case 3	Case 4	Case 5	*P* value
Initially Prednisone dose (mg/Kg/d)	1	0.8	1	1	0.8	
Follow up time (Month)	39	37	36	21	20	
Serum Creatinine (μmol/L)						
At renal biopsy	449	412	456	902	983	
one month of treatment	87	212	178	450	485	0.041*
Current	79	157	104	211	315	
plasma calcium	N	N	N	N	N	
Recurrent	No	No	No	Yes	No	

N: normal. * Creatine at renal biopsy vs. one month of treatment, $P=0.041$

renal interstitial acute inflammation and chronic fibrosis is helpful in determining the severity of the disease. Glucocorticoids significantly improves the clinical manifestations of sarcoidosis, normalizes hypercalcemia and decreases the serum creatine.

Currently, there is more detailed research into the pathological manifestations of pulmonary sarcoidosis. Pulmonary sarcoidosis is characterized by the presence of well-formed, discrete, non-necrotizing granulomas. These granulomas are composed of lymphocytes, which are surrounded by epithelioid histiocytes, multinucleated giant cells, plasma cells, and fibroblasts in the periphery. The central portion of the granuloma consists of predominantly CD4+lymphocytes, whereas CD8+lymphocytes are present in the peripheral zone [2, 11–13]. IHC was used in this study to identify the inflammatory cellular components of diffuse infiltrate in granulomatous lesions. This is the first time that IHC has been performed in granulomas of RS. We found that the granuloma was primarily composed of T lymphocytes, with CD4+T cells located in the central region and CD8+T cells surrounding the periphery. This is consistent with the pathological manifestations of pulmonary sarcoidosis. The distribution of different T-cell types was correlated with the pathogenesis of sarcoidosis. Sarcoid granulomas form in response to a persistent antigenic stimulus that is unlikely to be properly degraded, inducing a local Th1-type T cell (CD4+) mediated immune response. As a result of their chronic stimulation, macrophages release inflammatory mediators locally, leading to an accumulation of Th1 cells at sites of ongoing inflammation and contributing to the development of the granuloma structure, which can lead to fibrosis in persistent disease. There is a shift in the cytokine pattern from a Th1 to a Th2 phenotype with secretion of IL-4, IL-5, IL-6, IL-9, and IL-10 [12].

For the first time, we present a semi-quantitative score for assessing the degree of pathological inflammation in RS. This score comprehensively reflects the severity of tubular necrosis, interstitial inflammation, and fibrosis, and can serve as a clinical basis for informing treatment decisions [14, 15]. The initial treatment for sarcoidosis is glucocorticoids, the most effective, rapid-acting and available drug. It's the first line of treatment [1, 16–18]. The optimal prednisone dose and duration of prednisone for RS is not standardized. As the grade of acute

renal interstitial inflammation increases, the severity of the disease escalates, necessitating the prompt initiation of glucocorticoid treatment. Conversely, a higher grade of renal interstitial chronic fibrosis indicates a more chronic disease state, potentially resulting in a diminished response to glucocorticoids and an increased risk of persistent renal insufficiency. It is recommended to start steroid therapy early in order to manage renal fibrosis effectively. As there is an excellent response to corticosteroid therapy even in patients with severe progressive renal failure, confirmation of RS is an important diagnostic workup [19–22]. In our study, the serum creatinine levels of Cases 1, 2, and 3 were approximately 400 μmol/L, and the renal pathological inflammation grade was low. By the conclusion of the follow-up period, the recovery of renal function in these three patients was relatively satisfactory. In contrast, Cases 4 and 5 presented with blood creatinine levels exceeding 900 μmol/L at the time of diagnosis, accompanied by a high pathological inflammation grade. Case 4 experienced a recurrence of the disease, and the recovery of renal function in these two patients was poor. So, the semi-quantitative grading scores of acute inflammation and chronic fibrosis in renal pathology, in conjunction with the serum creatinine level at the onset of the disease, may aid in evaluating the long-term renal prognosis.

Glomerular ischemic sclerotic lesions deserve further discussion. Vascular lesions resulting from hypertension and diabetes can lead to glomerular ischemic sclerosis. Notably, only case 2 had a history of hypertension and diabetes prior to onset. The other three patients (cases 3, 4, and 5) all exhibited glomerular ischemic sclerosis without a clear history of hypertension or diabetes. We hypothesize that this condition may be linked to the infiltration of a significant number of inflammatory cells within the renal interstitium. These lesions can impact the blood vessels in the renal interstitium, thereby leading to glomerular ischemic sclerosis. It is important to note that the proportion of glomerular ischemic sclerosis observed in the second renal biopsy of case 4 was lower than that in the initial biopsy, which is attributed to potential sampling biases in renal biopsy specimens. The pathology from the repeated renal biopsy indicated a significant progression of renal interstitial fibrosis compared to the earlier assessment, reflecting chronic symptoms. Severe renal interstitial fibrosis can lead to glomerular ischemia and shrinkage, resulting in a sparse distribution of glomeruli. Consequently, the reduced total number of glomeruli and the lower ischemic sclerosis ratio in the second renal biopsy can be linked to these factors.

Diseases that may demonstrate eosinophilia on renal pathology are mainly allergic interstitial nephritis and IgG4-associated nephropathy, whereas in the present study we found that eosinophilic cells were also seen on renal pathology in patients with RS, as reported in Francesco's study [21]. However, the exact mechanism is still unclear. Sarcoidosis is believed to be caused by prolonged exposure to unidentified antigens, which triggers the accumulation of CD4+T cells and the secretion of diverse cytokines like IL-5. This cytokine plays a role in promoting the development of eosinophils and controlling eosinophilic inflammation [23]. It is thought that this may be the mechanism by which there is eosinophilic infiltration in the pathology of nodular disease.

A male predominance was observed in RS, despite reports that sarcoidosis is more common in females (30% more than males) [24–26]. This finding is consistent with several studies of renal sarcoidosis [6, 27], which predict that males are more likely to have renal involvement. The specific mechanisms behind the apparent gender differences in RS are currently unclear.

We found that patients with RS had prominent hypercalcemia. Hypercalcemia is present in 10–17% of patients with sarcoidosis [16]. The reported incidence of hypercalcemia in studies of biopsy-proven RS ranges from 23.4–37.5% [6, 27, 28]. However, in our study, the prevalence of hypercalcemia was 60%, which is significantly higher than previously reported in the literature. Higher level of serum calcium can lead to calcium salt deposits in kidney tissue and damage kidney function [18]. The reason for renal biopsy in all patients in this study was AKI, and two patients had significant bone pain and hypercalcemia. Therefore, it is believed that there is a selection bias that leads to an unusually high percentage of patients with hypercalcemia in this study.

The limitations of this study include its single-center design and small sample size. RS is a rare disease with a low incidence rate. Future multi-center studies are necessary to increase the sample size and further validate the clinical value of the renal interstitial grading score in the accurate diagnosis of RS. The prognosis of the patients in this study was heterogeneous. Except for one patient with disease recurrence who underwent a repeat renal biopsy, the remaining patients did not consent to additional renal punctures. It can only be inferred from the treatment that patients with higher creatinine levels at onset and pathological manifestations of GTIN have a worse prognosis. In the future, we will place greater emphasis on the implementation of repeated renal biopsies to better assess prognosis and guide treatment based on the dynamic evolution of pathology.

Conclusion

RS is uncommon and has no specific clinical manifestations. RS should be considered in the setting of hypercalcemia and acute renal failure. Renal biopsy remains the gold standard for diagnosis. Semi-quantitative grading scores provide a means to quantify information regarding

interstitial inflammation, as well as tubular and chronicity indices. The lymphocyte composition of granulomas is predominantly CD4+T cells in the center and CD8+T cells in the periphery. Steroid therapy is effective in suppressing active inflammation, improving renal function and preventing residual chronic kidney disease. However, it is important to monitor for recurrence and consider a second kidney biopsy if necessary.

Author contributions
Aichun Liu collected the clinical data and wrote the manuscript. Yina Wang, Yan Yu, Bao Dong and Meishun Cai were responsible for the work in the field of renal pathology. Yina Wang and Li Zuo reviewed and revised the manuscript.

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Data availability
No datasets were generated or analysed during the current study.

Declarations

Competing interests
The authors declare no competing interests.

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