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Case report

Acute kidney injury as a rare manifestation of pediatric sarcoidosis: A case report and systematic literature review

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ABSTRACT

Background: Sarcoidosis is a chronic noncaseating granulomatous disease with an unknown etiology that can affect multiple organs. Renal involvement in pediatric-onset adult-type sarcoidosis is rare, and only a few cases have been reported. We present a case of a Chinese patient with pediatric-onset adult-type sarcoidosis with renal involvement, and a literature review was performed.

Methods: The PubMed database was searched for publications, and relevant clinical data were extracted and presented.

Results: We identified 22 pediatric-onset adult-type sarcoidosis cases with renal involvement. Acute kidney injury was the major clinical presentation. Granulomatous interstitial nephritis was the predominant histopathological feature. All patients were treated with corticosteroids and immunosuppressive agents, and most achieved improved outcome.

Conclusions: Sarcoidosis should be considered in children with acute kidney injury of an unknown etiology. A final diagnosis is established through a combination of the clinical and laboratory characteristics, radiological presentation, and histological features of noncaseating granulomas. A therapeutic schedule should be decided after a systemic assessment.

1. Introduction

Sarcoidosis, a multisystem disorder, is characterized by noncaseating granulomas [1]. In the United States and Europe, the prevalence of pediatric-onset adult-type sarcoidosis (< 15 y) is 0.22–0.27 cases per 100,000 children [2]. Sarcoidosis is classified into two distinct forms in children, including early onset sarcoidosis and pediatric-onset adult-type sarcoidosis. Early onset sarcoidosis is characterized by a triad consisting of uveitis, arthritis and rash and is mainly caused by NOD2 mutation [3]. Pediatric-onset adult-type sarcoidosis preferentially involves the lung and mediastinum. Renal involvement is rare and often leads to a delayed diagnosis [4]. However, an early diagnosis and response to treatment are the prognostic factors for renal survival.

2. Materials and methods

A patient with pediatric-onset adult-type sarcoidosis with kidney involvement was diagnosed in Children's Hospital of Fudan University. Clinical data were collected and analyzed.

The PubMed database was searched for the all publications with the keywords or MeSH terms “renal sarcoidosis”, “granulomatous interstitial nephritis”, “renal sarcoidosis” or “granulomatous interstitial nephritis” AND “pediatric” or “child”. Only English language articles were included. We also searched the Chinese Journal Full-text Database (CNKI) using the same keywords in Chinese. Patients with early onset sarcoidosis with renal involvement were excluded.

Pediatric-onset adult-type sarcoidosis with renal involvement is uncommon in pediatric patients; only a few case studies have been published in English, and we performed a literature review of the available English publications.

Abbreviations: GIN, granulomatous interstitial nephritis; AKI, acute kidney injury; CRP, c-reactive protein; ESR, erythrocyte sedimentation rate; ACE, angiotensin-converting enzyme; MMF, mycophenolate mofetil; CYC, cyclophosphamide; MTX, methotrexate; AIN, acute interstitial nephritis; ^{18}F-FDG PET/CT, ^{18}F-FDG positron emission tomography/computed tomography

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We confirm we obtained the patient's written informed consent for the publication of the material without identifying details. We also declare that our publication was approved by the ethics board of Children's Hospital of Fudan University.

3. Results

3.1. Case report

A 10-y previously healthy Chinese male was admitted to our hospital with intermittent fever for > 1 month and AKI for approximately 20 days. He also suffered intermittent abdominal pain with nausea and vomiting. Some tests previously performed in a local hospital revealed anemia, a slightly elevated c-reactive protein (CRP) level and erythrocyte sedimentation rate (ESR), and a significantly increased serum creatinine (Scr) concentration. Doppler ultrasound of the kidney showed normal-sized kidneys with increased parenchymal echogenicity. A computed tomography (CT) scan of the chest and abdomen revealed hilar lymphadenopathy, bilateral pneumonia and hepatosplenomegaly. The patient failed to respond to treatment with antibiotics and was transferred to our hospital.

Upon admission, a physical examination revealed a height and weight of 145 cm (50th percentile) and 29 kg (25th percentile), respectively, and the patient's body temperature and blood pressure were 37.0 °C and 95/50 mmHg, respectively. He presented pallor, lymphadenectasis of the inguinal and cervical regions, and hepatosplenomegaly. A physical examination showed no other remarkable findings. No potentially harmful medications were ever administered, and he had no history of tuberculosis (TB) and no known TB contacts. His family history was also unremarkable.

Table 1 lists the critical laboratory data obtained after being transferred to our hospital. A complete blood cell count showed leukopenia and anemia. The CRP level and ESR were moderately elevated. A biochemical analysis revealed significantly elevated Scr, blood urea nitrogen and cystatin C levels. His liver function was normal when he was transferred but deteriorated during his stay before treatment, which is described later. His serum calcium and 25-dihydroxyvitamin D levels were normal. A urinalysis showed proteinuria, and a urine microprotein analysis illustrated that the α1 macroglobulin level was significantly elevated, which indicated tubulointerstitial lesions. The serum calcium level and urine calcium-to-creatinine ratio were approximately normal. Renal ultrasound showed normal-sized kidneys with increased parenchymal echogenicity but no evidence of nephrolithiasis or nephrocalcinosis. An abdominal ultrasound showed hepatosplenomegaly and enlarged peripheral lymph nodes. A pulmonary CT scan indicated diffuse pulmonary infiltration with nodules and bilateral hilar lymphadenopathy (Fig. 1). The cranial MRI and echocardiogram were normal. An eye slit lamp examination and dilated fundoscopy were performed by an ophthalmologist, and the results were normal.

After a preliminary evaluation, the patient was diagnosed with AKI with multiorgan involvement. The pathogenesis of AKI is complicated, and the further differential diagnosis is shown in Fig. 2. The main causes of AKI are drug-induced damage and infection-related diseases. As no potential harmful medications were administered before renal function deteriorated, also the peripheral eosinophilia and drug eruption were absent, the possibility of a medication-related cause was excluded. Infection-related diseases are a major cause of AKI that act through a mechanism that involves insufficient perfusion of the kidneys and inflammatory reactions. Infection markers were examined to exclude the possibility of infection-related diseases. Procalcitonin and interleukin-6 levels were slightly higher than normal. Both blood and sputum cultures were negative. IgMs against cytomegalovirus and the Epstein-Barr virus were negative, and the (1,3)-β-D-glucan (G) test (G-test), which detects fungal infection, was also negative. The results of the tuberculin skin test and Mycobacterium tuberculosis T cell spot test (T-SPOT) were negative; the results of human immunodeficiency virus and syphilis tests were also negative. Infection-related diseases were unlikely based on the results from the aforementioned examinations. Additionally, primary immunodeficiency disorders and connective tissue diseases are uncommon causes of AKI. Moreover, the results of immune function tests were within the normal ranges, including immunoglobulins (IgG, IgA, and IgM), IgG subtypes (IgG1, IgG2, IgG3, and IgG4), serum levels of complement proteins (C3, C4, and CH50), $CD4^+$T lymphocytes, $CD8^+$ T lymphocytes, $CD16^+56^+$ cells and the CD4 + /CD8 + ratio. Furthermore, anti-nuclear antibodies, anti-glomerular basement membrane antibodies, extractable nuclear antigens, and anti-neutrophil cytoplasmic autoantibodies (ANCAs) were negative, which excluded the possibility of common primary immunodeficiency disorders, and thus, connective tissue diseases were unlikely.

However, during the first 2 weeks following admission, the patient's renal function steadily deteriorated, and severe leukopenia occurred. Although We excluded the possibility of leukemia according to the bone marrow aspiration result, the CT scan of the chest and lymphadenectasis still strongly suggested the possibility of solid tumors. An ^{18}F-fluorodeoxyglucose (FDG)-positron emission tomography (PET)/CT scan was further performed, which revealed increased uptake of FDG within the hilar and multiple peripheral lymph nodes, liver and spleen (SUV 2.1–5.4). Lymphoma was strongly suspected, and further biopsies of the pulmonary system, spleen, kidney and peripheral lymph nodes were considered. We prioritized an inguinal lymph node biopsy considering the relatively poor pulmonary function and high risk of bleeding, which revealed noncaseating granulomas without malignant cells, acid-fast bacillus and fungus (Fig. 3). A percutaneous renal biopsy was also performed to confirm the etiology of the AKI, which revealed multinucleated giant cell infiltration and severe noncaseating epithelioid granulomas, with calcification in occasional granulomas. The biopsy also revealed hypertrophy in proximal tubule epithelial cells, without any remarkable glomerular lesions or any abnormalities in the immunofluorescence examination (Fig. 4). These pathological features were strongly suggestive of sarcoidosis. Consistent with these features, the serum angiotensin-converting enzyme (ACE) concentration was measured and was significantly elevated. Finally, sarcoidosis was diagnosed with the involvement of the kidney, lung, lymph node and liver. In addition, whole-exon sequencing of a blood sample did not detect any pathogenic mutations.

The patient's liver function deteriorated during his two-week stay before he was finally diagnosed with sarcoidosis and treated. The deterioration in liver function (Table 1) may have been caused by sarcoidosis. We prescribed oral prednisolone (2 mg/kg/day, 50 mg/day) and mycophenolate mofetil (MMF, 0.5 g, q 12 h). After two weeks of treatment, the fever and abdominal pain subsided. The white blood cell counts, hemoglobin levels, and liver and pulmonary functions returned to normal (Table 1). ACE levels returned to a normal range after 8 weeks. The serum creatinine level gradually decreased to 91 μmol/l as prednisone was tapered to a daily dose of 25 mg. The patient underwent regular follow-up, but serum creatinine levels were maintained at 91 μmol/l. Then, we discontinued MMF and prescribed monthly intravenous pulse therapy with cyclophosphamide (CYC, 600 mg/month). The patient's renal function improved after two months of treatment, and the steroid dose was then gradually tapered (Fig. 5).

3.2. Literature review

Pediatric-onset adult-type sarcoidosis can affect any system, and > 90% of patients present with pulmonary infiltration and hilar adenopathy, 43% of patients exhibit hepatomegaly and splenomegaly, > 60% of patients display eye involvement, and < 10% of patients present with renal involvement [5]. We performed a literature review and identified 22 pediatric-onset adult-type sarcoidosis cases with renal involvement. Table 2 shows the major features of these cases

Table 1
Relevant laboratory results before and after treatment.

	Testing at transfer	Testing before treatment	Testing after treatment	Normal range
Complete blood count				
WBC	3.8	2.1	6.2	(4–10)*10^9 cells/l
N	52.3%	40.7%	70.5%	
Hb	85	78.2	127	110–160 g/l
CRP	< 8	12	< 8	< 8 mg/l
ESR	20	30	15	0–20 mm/h
Procalcitonin	0.08	–	0.04	< 0.05 ng/ml
interleukin-6	5.59	–	6.26	< 7 pg/ml
T-Spot	Negative	–	Negative	Negative
G test	49.5	–		< 100.5 pg/ml
LPS	0.0376	–		< 0.053 EU/ml
HIV & syphilis	Negative &Negative	–	Negative &Negative	Negative &Negative
Renal function				
Serum creatine	274	246	77	18–66 μmol/l
eGFR	19.3	21.5	67.4	> 90 ml/min/1.73 m^2
Blood urea nitrogen	9.1	10.8	5.5	2.5–6.5 mmol/l
CYSC	3.12	4.49	1.3	0.55–1.55 mg/l
Liver function				
Alb	36.1	36.1	42.9	38–54 g/l
ALT	5	983	12	5–40 U/l
AST	30	2192	22	15–60 U/l
Serum calcium	2.67	2.58	2.41	2.2–2.75 mmol/l
Proteinuria	±	1+	Negative	Negative
Urine NAGL	661	–	35.6	< 100 ng/ml
Urine microalbumin				
AIMU/CR	311.8	284.4	13.2	0–14 mg/g
ALBU/CR	39.9	37.2	13.8	0–26.5 mg/g
IGGU/CR	22.6	19.9	4.2	0–14 mg/g
NAG/CR	5.65	9	1.83	0.3–1.2 U/mmol
Urine protein at 24 h	0.93	1.25	0.12	< 0.14 g
Urinary calcium/creatine ratio	0.22	–	0.16	< 0.21
Tumor markers				
AFP	0.6	–	–	0–5.6 ng/ml
CEA	1.3	–	–	< 5.0 ng/ml
FERR	235.9	–	52.1	9.94–71.7 ng/ml
NSE	27.17	–	–	0–16.3 ng/ml
Immune function				
IgG	15	–	9.3	6.09–12.85 g/l
IgA	3.93	–	1.98	0.52–16 g/l
IgM	1.11	–	0.5	0.67–2.01 g/l
IgE	353	–	0.82	< 100 KU/l
CD4	35.71%	–	36.87%	29–36%
CD8	23.47%	–	34.81%	24–34%
CD4/CD8	1.52	–	1.06	
1,25-Dihydroxyvitamin D	20.17	–	–	15–35 ng/ml
ACE	–	127.8	14	20–112 U/l

Abbreviations: ESR: erythrocyte sedimentation rate, G test: (1,3)-β-D-glucan test, T-Spot: *Mycobacterium tuberculosis* T cell spot test (T-SPOT), HIV: human immunodeficiency virus, AFP: alpha fetoprotein, CEA: carcinoembryonic antigen, FERR: ferritin, NSE: neuron-specific enolase, -: not determined.

[6–15]. The patients' ages ranged from 9 to 17 y, and most of the patients (85%) presented with multiorgan involvement including the eyes, lungs and lymph nodes. Notably, 10% of these patients presented isolated renal involvement and were diagnosed by kidney biopsy, while 73% of patients presented with AKI.

We analyzed the data obtained from these reports, although a detailed differential diagnosis was not explicitly described in most cases. First, critical laboratory data were collected and analyzed to confirm the affected organs. The main diseases considered in the differential diagnosis, including infection-related diseases and common connective tissue diseases, were excluded by detecting the levels of inflammation markers, anti-nuclear antibody, extractable nuclear antigen and ANCA. All laboratory tests were negative in these cases.

Abnormal calcium metabolism and high serum ACE activity (> 2 times the upper limit of normal) seemed to support a diagnosis of sarcoidosis. However, only 29% of these patients were found to have hypercalcemia, and 44% had elevated ACE levels. This result indicates that the specificity of ACE or hypercalcemia in the diagnosis of sarcoidosis is still unclear. Other markers/data from CD4/CD8 ratio tests are potentially positive but nonconclusive indicators as well.

Granulomatous interstitial nephritis (GIN) was a common renal pathological feature in these patients. Only a few patients presented with glomerular basement membrane or renal vascular involvement, with clinical manifestations indicative of nephrotic syndrome or hypertension, and two patients exhibited membranous nephropathy. Before the final diagnosis was performed, other causes of granulomatous interstitial nephritis, such as medication-related interstitial nephritis, Wegener's granulomatosis, tuberculous and fungal pyelonephritis, and tubulo-interstitial nephritis and uveitis (TINU) syndromes should be excluded by examining the clinical manifestation and laboratory test results.

All patients were treated with corticosteroids once sarcoidosis was diagnosed. Immunosuppressive agents (e.g., MMF, CYC, MTX, or infliximab) were administered to refractory patients in whom corticosteroids are difficult to taper or discontinue because of critical or progressive organ involvement or severe side effects associated with corticosteroids.

We also evaluated the outcomes of these reported cases. The time of follow-up ranged from 0.5 to 5.5 years. Fifteen of the 22 patients (68.2%) achieved complete/ partial remission, 6 of 22 progressed to

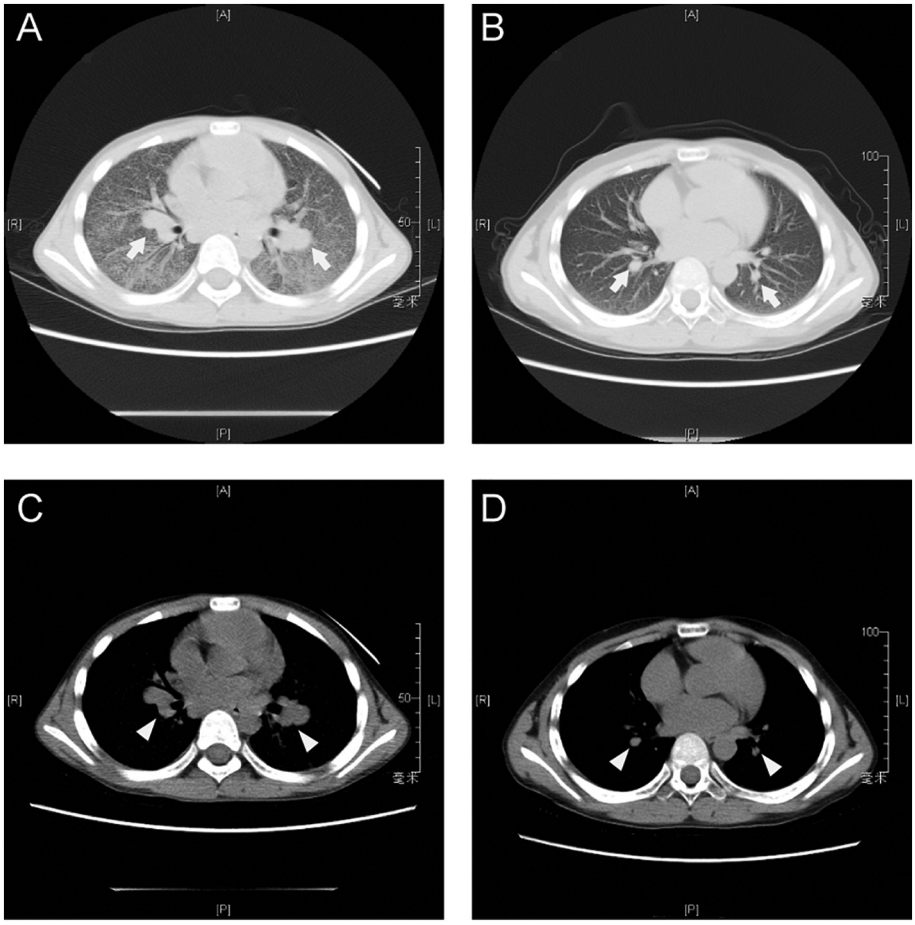

Fig. 1. Computed tomography of the chest. A and B: Lung windows before treatment and after a 6-month treatment period. C and D: Mediastinal windows before treatment and after a 6-month treatment period. The arrowhead shows the hilar lymph nodes.

chronic kidney disease/end stage renal disease, and only 1 patient died of a serious infection during treatment with infliximab.

4. Discussion

Here, we presented a case report of a 10-year-old Chinese boy with initial presentation of AKI, whose diagnosis was confirmed to be pediatric-onset adult-type sarcoidosis with multiple organ involvement. Renal involvement is fairly rare in patients with pediatric-onset adult-type sarcoidosis and only 22 pediatric cases have been reported. In these cases, AKI is the major clinical manifestation and granulomatous interstitial nephritis (GIN) is the predominant histopathological feature.

Sarcoidosis with extrapulmonary involvement is rare, which leads to a delayed diagnosis. The final diagnosis is based on a combination of the laboratory and radiological findings and the pathological features of noncaseating granulomata in affected tissues. A CD4/CD8 T cell ratio > 3.5 on bronchoalveolar lavage, abnormal calcium metabolism including hypercalcemia and hypercalciuria, and serum ACE activity > 2 times the upper limit of normal levels are supportive findings [16]. We recommend that ^{18}F-FDG PET/CT should be performed before the biopsy due to its importance for the detection of activated inflammatory and tumor cells and its ability to identify suitable biopsy sites. However, an evaluation of the kidney using ^{18}F-FDG PET/CT remains challenging, and thus, a renal biopsy is still essential to analyze

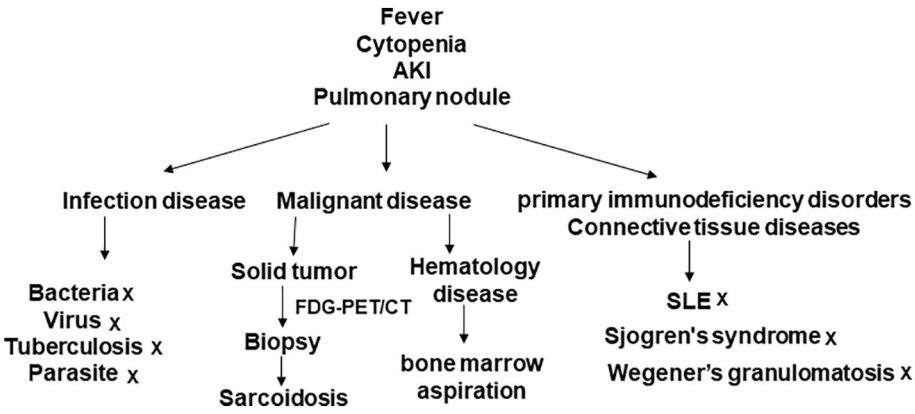

Fig. 2. The approach used for the diagnosis and differential diagnosis of our patient. X represents the excluded diseases.

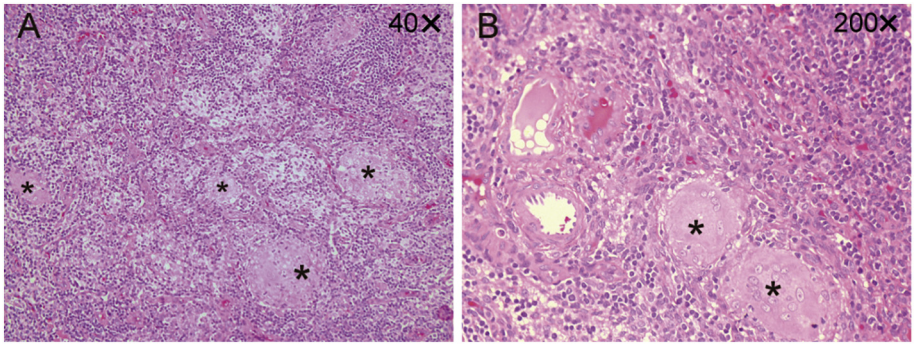

Fig. 3. Hematoxylin-eosin staining of a right inguinal lymph node biopsy. Stars show non-caseating granulomas (A, X40 and B, X200).

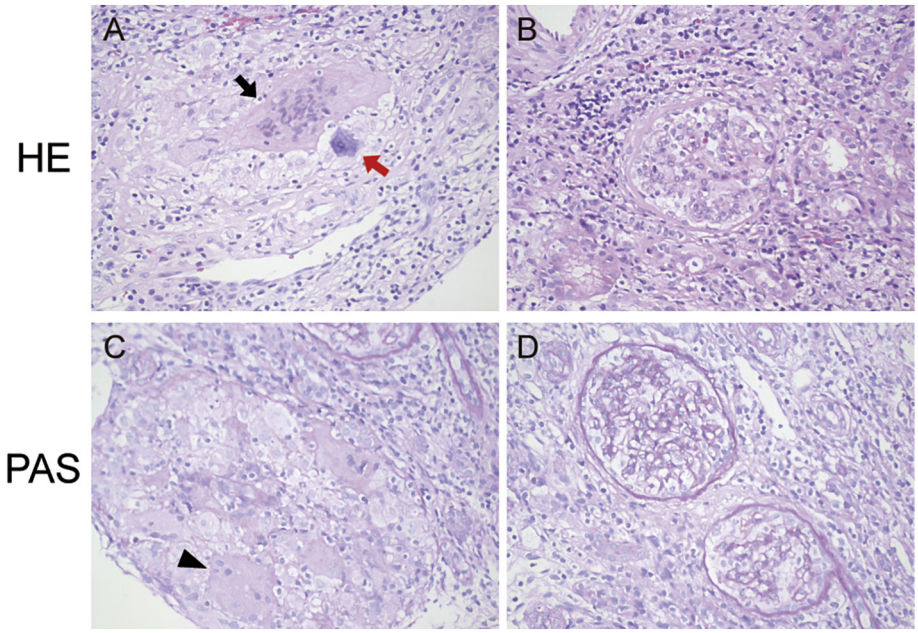

Fig. 4. Histopathology of a percutaneous renal biopsy. A and B: The black arrowheads show multi-nucleated giant cells, while red arrowheads show nephrocalcinosis. B: Lymphocyte infiltration in the renal interstitium (hematoxylin-eosin staining, x200). C and D: Hypertrophy of the proximal tubule epithelial cells is shown. The glomeruli and arterial walls were not affected, and no acid-fast bacilli or fungi were observed (periodic acid-Schiff staining, x200). Immunofluorescence microscopy and electron microscopy were normal. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

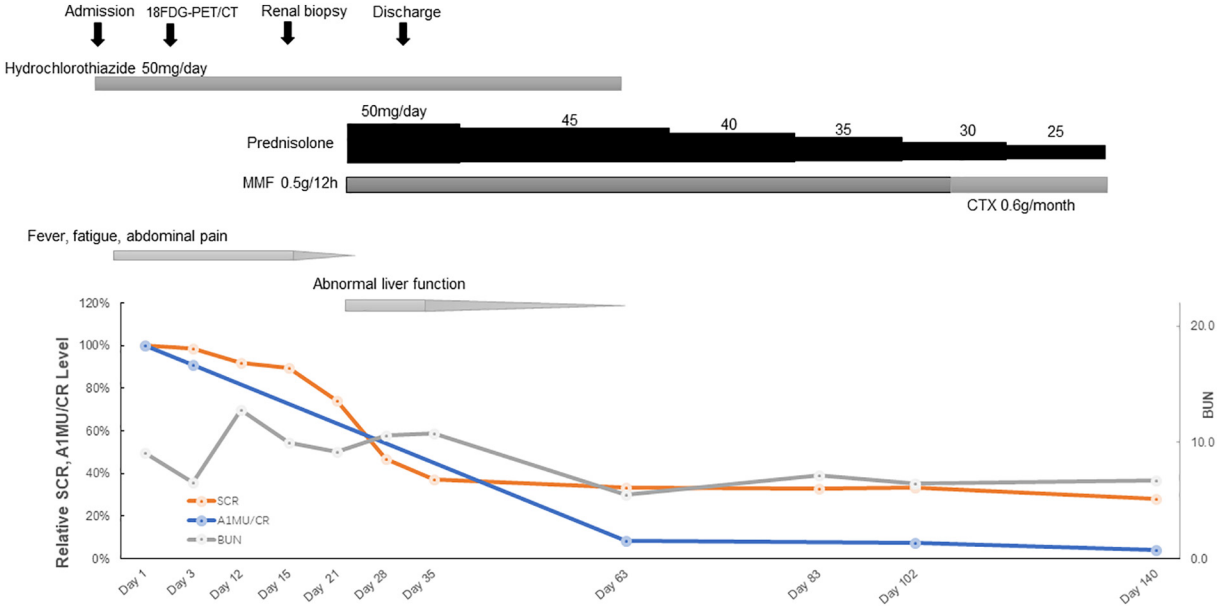

Fig. 5. Clinical cause of the manifestations and increased serum creatinine (Scr), blood urea nitrogen (BUN), and A1MU/CR levels in our patient before treatment and after therapy with corticosteroids and MMF/CYC.

Table 2
Reported cases of renal involvement in pediatric patients with sarcoidosis.

Reference	Our patient	[6]	[7]	[8]	[9]	[10]	[11]	[12]	[13]	[14]	[15]
Male/female ratio	M	6/5	F	M	M	M	M	M	M	M	NM
Age at onset (y)	10	10.1	13	15	14	17	9	13	14	14	NM
General symptoms		10/11									NM
Fever	+	/	+	−	−	+	−	−	−	−	
Fatigue	−	/	−	+	−	−	−	−	−	−	
Weight loss	−	/	+	+	−	−	−	−	−	−	
Renal manifestations											
AKI	+	+(9)		+	+			+	+	+	
NS			+								
Proteinuria	+	+(9)	+	+	−	+(β2MG)	+(β2MG)	+(1.2 g/d)	−	−	
Hematuria	−	+(4)	+	−	+	−	−	−	−	−	
Leukocyturia	−	+(7)	−	−	+	+	−	−	−	−	
Other organs involved	Lung, Liver, Spleen, Lymph node	Lung (6/11), Eye (6/11), Abdomen (4/11), Joints (3/11), Liver (7/11), Spleen (5/11)	Hilar adenopathy, Leg hepatosplenomegaly	N	Ear	Eye	Eye	N	Eye	Eye	NM
ACE	Elevated	6/11 elevated	Normal	Normal	Normal	Nm	Nm	Normal	Elevated	NM	NM
Serum calcium	Normal	1/11 elevated	NM	Normal	Normal	Elevated	NM	Elevated	Elevated	Elevated	NM
Renal pathology											
GIN	+	11/11	+	+	+	−	+	+	+	+	+(1)
Others		Glomerular fibrosis (4/11)	Membranous nephropathy			Sclerosing glomeruli		Granulomatous arteritis			Nephrocalcinosis (1), Membranous nephropathy (1)
Treatment											
Prednisone	+	+	+	+	+	+	+	+	+	+	+(3)
Cyclophosphamide			+								+(2)
MMF	+			+					+		
Infliximab								+			+(1)
others	CYC		MTX			Mizoribine	MTX, Humira			MTX	
Follow-up (years)	0.6	5.5	1.5	1.8	2	2	NM	0.8	1	1	
Outcome (kidney)											
Renal function	GFR 67.4 ml/min/1.73 m^2	CKD (2), ESRD (2), GFR > 80 ml/min/1.73 m^2 (7)	Proteinuria (−), Normal GFR	Scr 97 μmol/l	Scr 141 μmol/l	Scr 167 μmol/l	Improved β2MG	GFR 37 ml/min/1.73 m^2	GFR 75 ml/min/1.73 m^2	Approximately normal	Complete resolution (1), ESRD (1), death (1)

Abbreviation: NM: not mentioned; CKD: chronic kidney disease; AKI: acute renal injury; NS: nephrotic syndrome; ACE: angiotensin-converting enzyme; GIN: granulomatous interstitial nephritis; MMF: mycophenolate mofetil.

the etiology of AKI. The presence of noncaseating granulomata in tissues and the exclusion of other causes of granulomatous disease remain the gold standard for the final diagnosis.

Although serum ACE activity is thought to be a biomarker for the diagnosis and treatment of sarcoidosis; the sensitivity of ACE in diagnosing sarcoidosis is approximately 40% [17]. Meanwhile, serum ACE activity is heavily affected by insertion/deletion (I/D) polymorphisms in the ACE gene and should not be overestimated in individuals. However, patients with higher ACE levels also suffer from more severe cases of sarcoidosis [18]. In our patient, serum ACE levels were elevated and returned to normal after timely treatment, consistent with his improved clinical manifestations.

Renal involvement is usually caused by hypercalcemia or hypercalcemia with nephrocalcinosis. Abnormal calcium metabolism is one of the sarcoidosis pathogenesis [19]. Notably, 1,25-dihydroxyvitamin D (calcitriol) is autonomously produced by the macrophages of the granuloma and promotes the absorption of calcium into the lumen, where it acts to elevate serum calcium levels and/or increase hypercalciuria. Hypercalcemia induces vasoconstriction, which reduces the glomerular filtration rate (GFR) [20]. A high granuloma burden in the kidneys secondary to hypergammaglobulinemia also causes renal injury. The patient's initial presentation was AKI, but his serum calcium and 24 h urine calcium levels were normal. Combined with the renal histopathology data, we speculated that the high granuloma burden was the main cause of AKI in this patient.

Once a diagnosis of sarcoidosis is established, a systemic evaluation should be performed to develop a treatment proposal. While no evidenced-based treatment guidelines are available for most presentations of sarcoidosis, the cornerstone treatment is corticosteroids, which have shown efficacy in treating GIN. Immunosuppressive agents (e.g., MMF, CYC, and MTX) should be used to treat patients with critical or progressive organ involvement or to reduce the side effects of exposure to corticosteroids [21]. In recent years, infliximab, an antagonist of tumor necrosis factor alpha (TNF-α), has been shown to display better efficacy as a treatment for refractory sarcoidosis. Because of infectious side effects, it should be used with caution [22]. According to the literature review, most patients with pediatric-onset adult-type sarcoidosis with renal involvement have a relatively good prognosis (Table 2).

In conclusion, pediatric-onset adult-type sarcoidosis with renal involvement is rare and can cause AKI by inducing hypercalcemia and/or GIN. We suggest that sarcoidosis should be considered in the differential diagnosis of pediatric patients with AKI of an unknown etiology, although a renal biopsy is necessary to clearly define the etiology. An early diagnosis, systemic assessment, and timely treatment with corticosteroids and/or immunosuppressive agents could result in a better prognosis.

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Authors' contributions

All authors participated in the diagnostic procedures. Chunyan Wang analyzed and interpreted the patient's data, Chunyan Wang performed the literature review and drafted the manuscript, Chunyan Wang and Tao Zhang completed the long-term follow up of the patient, Li Sun designed and supervised the study, Haimei Liu performed the kidney biopsy, Hong Xu reviewed the article, Jin Shen processed the radiological data, and Jiayan Feng performed the histological examination of the lymph nodes and kidney. All authors have read and approved the final manuscript.

Conflicts of interest

The authors have no competing interests to declare.

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