B-cell lymphoblastic lymphoma-associated renal damage: A case report and literature review

YONGHONG JIAN, GUOHUA DING, DINGPING YANG and JUAN DU

Department of Nephrology, Renmin Hospital of Wuhan University, Wuhan, Hubei 430060, P.R. China

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Abstract. Lymphoblastic lymphoma (LBL) is a highly malignant form of lymphoma with rapid progression and high mortality. According to the World Health Organization immunophenotype, it is classified into T-lymphoblastic lymphoma (T-LBL) and B-lymphoblastic lymphoma (B-LBL). B-LBL often involves lymph nodes and extranodal locations, such as the skin, bones, and soft tissues. However, renal damage as an initial symptom is very rare in B-LBL. The present study presented a rare case of renal involvement in a 30-year-old male patient with B-LBL presenting with acute renal failure with bilateral renal enlargement. Renal involvement is rare in B-LBL, and nephrologists should improve the understanding of this disease.

Introduction

Non-Hodgkin lymphoma (NHL) usually originates from lymphoid tissues and may involve other organs, such as the stomach, intestines, lungs, breasts and kidneys. Autopsy findings have indicated that ~30-50% of NHL patients have renal involvement, which occurs in the late stage of the disease, is usually asymptomatic and is rarely diagnosed before mortality. Overall, 0.9-23% of such cases progress to renal failure (1), but renal damage as an initial symptom of lymphoma is very rare (2). Renal involvement may manifest as a renal mass or invasive kidney disease. Pathologically, renal involvement is characterized by diffuse large B-cell lymphoma (3) and, very rarely, B-LBL. The present study reported the clinical data for a patient with lymphoma-associated renal damage whose initial symptoms included acute renal failure and bilateral renal enlargement and the pathological results confirmed B-LBL.

Correspondence to: Dr Juan Du, Department of Nephrology, Renmin Hospital of Wuhan University, 238 Jiefang Road, Wuchang, Wuhan, Hubei 430060, P.R. China
E-mail: cuckoo.du@qq.com

Abbreviations: LBL, Lymphoblastic lymphoma; T-LBL, T-lymphoblastic lymphoma; B-LBL, B-lymphoblastic lymphoma; NHL, non-Hodgkin lymphoma; B-ALL/LBL, B-lymphoblastic leukemia/lymphoma

Key words: non-Hodgkin lymphoma, B-cell lymphoblastic lymphoma, acute kidney injury, bilateral renal enlargement, B-cell lymphoblastic lymphoma-associated renal damage

Case presentation

A 30-year-old male patient presented with unexplained leg pain, weight loss and intermittent fever for more than one month. He was then admitted to the Renmin Hospital of Wuhan University due to the discovery of abnormal kidney function on October 11, 2019. His history of past illness was as follows. Other than intellectual disability, the patient was healthy, as were his parents.

Physical examination upon admission revealed elevated blood pressure (BP146/96 mm Hg) as the only positive result. From the laboratory examination, the following results were obtained. Blood routine (automatic blood cell analyzer; XN-9000; Sysmex Europe SE) showed a white blood cell count (WBC) of $8.96x10^9$/l, neutrophil count (Neu#) of $6.42x10^9$/l, lymphocyte count (LYM#) of $1.55x10^9$/l, and hemoglobin (Hb) of 93 g/l (Table I). Blood chemistry (biochemistry analyzer; ADVIA 2400/1800/Chemistry XPT; Siemens AG) indicated a urea level of 12.48 mmol/l, creatinine level of 312 μmol/l, and an estimated glomerular filtration rate of 21.89 ml/min. Urine analysis (full-auto urine sediment analyzer; UF-5000; Sysmex Europe SE) showed blood 1+ and a 24-hour urinary total protein level of 0.19 g. The erythrocyte sedimentation rate (Ves-matic cube; TEST1; Diesse Diagnostica Senese S.p.A.) was 120 mm/h. Humoral immunity (Immune analyzer; IMMAGE800; Beckman Coulter, Inc.) indicated an immunoglobulin E level of 884 IU/ml, a C4 level of 0.445 g/l, an IgG4 level of 4.26 g/l. Moreover, antinuclear antibodies and extractable nuclear antigens (fluorescence microscope; EUROStar), antineutrophil cytoplasmic antibodies (fluorescence microscope; EUROStar), anti-glomerular basement membrane (automatic enzyme immunoassay analyzer; Alegria; ORGENTEC Diagnostika), cytomegalovirus and Epstein-Barr virus (PCR; AGS4800; Daan Gene Co., Ltd.) were negative. Urinary Doppler ultrasound showed bilateral renal enlargement (left kidney 15.7x8.9 cm, parenchymal thickness 2.5 cm; right kidney 14.4x8.3 cm, parenchymal thickness 2.6 cm). No swollen lymph nodes were detected with ultrasound or computed tomography (CT).

First, it was considered that the patient might have had acute interstitial nephritis. To avoid treatment delays,

methylprednisolone (40 mg/d, intravenous drip) was added empirically on October 14. Then, renal biopsy was performed for the patient. The results indicated severe acute renal interstitial lesions and a large number of interstitial lymphocytes with a uniform morphology. Renal cortices were minced into 1 mm^3 pieces and fixed with glutaraldehyde followed by osmic acid. Ultrathin sections (40-60 nm) were stained with lead citrate and alcoholic uranyl acetate for 10 minutes and electron microscopy (TEM) imaging (Hitachi, Japan). The result also revealed a small amount of renal tissue and a large number of lymphocytes that were morphologically uniform and immature (Fig. 1). The kidney tissues were fixed overnight at 4˚C in 4% paraformaldehyde, embedded in paraffin and sectioned. The sections were dewaxed and hydrated in sequence, and then antigen retrieval was performed using sodium citrate buffer at ~100˚C for 30 min. Subsequently, the tissue sections were incubated with 5% normal goat serum for 20 min and incubated overnight at 4˚C with corresponding primary antibody (Maixin Biotechnology; 1:100). Then, the sections were incubated with HRP-conjugated secondary antibody (Maixin Biotechnology; 1:200) at room temperature for 30 min. Finally, images were captured under a light microscope (Olympus, Japan).The result showed lymphoid cells positive for cluster of differentiation (CD)3 (scattered), CD20 (focal), Ki67 (60%), Pax 5, CD10, and TdT but negative for CD23, Bcl-6, Mum1, Bcl-2, CD5, P53, and CD30 (Fig. 2). The patient was diagnosed with B-cell lymphoblastic lymphoma (B-LBL)-associated renal damage. To further identify the primary lymphoma lesion, the patient underwent bone marrow aspiration and positron emission tomography (PET)-CT. Reverse transcription quantitative PCR technology was used to screen leukemia fusion genes and the result showed the E2A-PBX1 fusion gene (+). The immunophenotyping of leukemia as detected by flow cytometry (BD FACSCanto II; BD Biosciences) revealed elevated abnormal cells (immature B cells), suggesting the possibility of precursor B-cell acute lymphoblastic leukemia (B-ALL). Bone marrow was taken for smearing and Wright-giemsa staining and then observed under a microscope. The results indicated elevated proliferation of nucleated cells in the bone marrow. Specifically, the leukocyte-to-erythrocyte ratio was 1.58:1, granulocytes accounted for 28.5% of cells, and promyelocytes (and later-stage cells) were visible; most granulocytes were neutrophils with rod-shaped nuclei and a largely normal morphology. Erythrocytes accounted for 18% of cells; proerythroblasts (and later-stage cells) were visible and were mostly metarubricytes; and mature erythrocytes varied in size and morphology. Lymphocytes accounted for 52% of cells; of these, lymphoblasts accounted for 29.5% of cells, and prolymphocytes accounted for 9.5% of cells. These data suggested the possibility of acute lymphoblastic leukemia and lymphoma. Bone marrow aspiration revealed an extremely high level of myeloproliferation (90%), suppression of three lineages of hemopoietic cells (granulocytes, erythrocytes and megakaryocytes) and diffuse, patchy type I cell proliferation. Combined with the patient's immunohistochemistry, these results suggested B-cell-derived leukemia/lymphoma. However, the immunohistochemistry results were unsatisfactory despite multiple attempts (Fig. 3). Immunohistochemistry showed CD10 (+), CD19 (weak +), CD20 (scattered +), CD23 (-), CD3 (-), CD34 (-), CD5 (-), CD79α (-), TdT (-), Pax-5 (weak+), lymphoid enhancer factor (LEF)1 (scattered+), Mum-1 (-), Bcl-6 (-), myeloperoxidase (MPO) (-), Cyclin-D1 (-), Kappa (-), Lambda (-), and Ki67 (labeling index indicating low proliferation). PET-CT revealed bilateral diffuse renal enlargement with increased metabolism, increased metabolism of the left and right psoas major muscles, increased metabolism of the lymph nodes next to the left iliac vessels, and extensive localized bone metabolism throughout the body (Fig. 4). The final diagnosis was B-LBL, stage IV, with associated renal damage (renal interstitial infiltration). Regular tests indicated gradual improvement in renal function. On October 28, a laboratory test showed a serum creatinine (Scr) of 107 μmol/l.

Once diagnosed, the patient was transferred to the Department of Hematology for further treatment; however, the patient requested discharge due to financial reasons and continued to take steroids with tapering after discharge. Once the steroids were withdrawn, he developed generalized pain and fever. On December 1, 2019, he was transferred to the Department of Hematology of Renmin Hospital of Wuhan University again due to uncontrolled conditions. Blood tests showed a WBC of 26.26x10^9/l, a Neu% of 3.6%, an LYM% of 6.9%, a Neu# of 7.88x10^9/l, an LYM# of 9.32x10^9/l, an Hb level of 96 g/l, and a platelet (PLT) count of 33x10^9/l. Blood chemistry indicated a urea level of 18.9 mmol/l, an Scr level of 289 μmol/l, a uric acid (UA) level of 1260 μmol/l, a lactate dehydrogenase (LDH) level of 4459 U/l, and a procalcitonin (PCT) level of 9.8 ng/ml. Throat swabs showed gram-positive cocci and bacilli. In consideration of concomitant infection, the patient was given low-dose intravenous dexamethasone and anti-infective treatment instead of standard chemotherapy. On December 16, blood tests showed a WBC of 62.6x10^9/l, a Neu# of 1.83x10^9/l, an LYM# of 12.36x10^9/l, an Hb level of 70 g/l, and a PLT count of 13x10^9/l, suggesting disease progression and the need for chemotherapy. Chemotherapy with anti-infective support was suggested to the patient since the patient's infection was serious, but the patient and his family members eventually discontinued treatment. The diagnosis at discharge included lymphoma cell leukemia and B-LBL with associated renal damage (renal interstitial infiltration).

The present study was carried out in accordance with the code of Ethics of the World Medical Association (Declaration of Helsinki) for experiments involving humans. It was reviewed and approved by the ethics committee of Renmin Hospital of Wuhan University (Wuhan, China; approval no. WDRY2021-KS015).

Discussion

In cases of lymphoma, renal involvement is known as secondary renal lymphoma with evidence of extensive lymph node or extranodal lymphoma or as primary renal lymphoma in the absence of other organ involvement (i.e., in cases with only renal involvement) (4). Primary renal lymphoma is very rare, accounting for <1% of extranodal lymphomas (5). Some researchers have speculated that primary renal lymphoma may originate from the renal capsule, which is rich in lymphoid tissue that can penetrate the renal parenchyma (6). In the present study, primary renal lymphoma was excluded because bone marrow aspiration and PET-CT found infiltration on organs other than the kidney.

Table I. Laboratory findings of the patient.

Parameter	2019.10.11	2019.12.01	2019.12.16
White blood cell count	$8.96x10^9$/l	$26.26x10^9$/l	$62.6x10^9$/l
Neutrophil count	$6.42x10^9$/l	$7.88x10^9$/l	$1.83x10^9$/l
Lymphocyte count	$1.55x10^9$/l	$9.32x10^9$/l	$12.36x10^9$/l
Hemoglobin	93 g/l	96 g/l	70 g/l
Platelet	$145x10^9$/l	$33x10^9$/l	$13x10^9$/l
Urea	12.48 mmol/l	18.9 mmol/l	-
Creatinine	312 μmol/l	289 μmol/l	-
Uric acid	616.00 μmol/l	1,260 μmol/l	-
Lactate dehydrogenase	774 U/l	4,459 U/l	-
24-hour urinary total protein	0.19 g	-	-

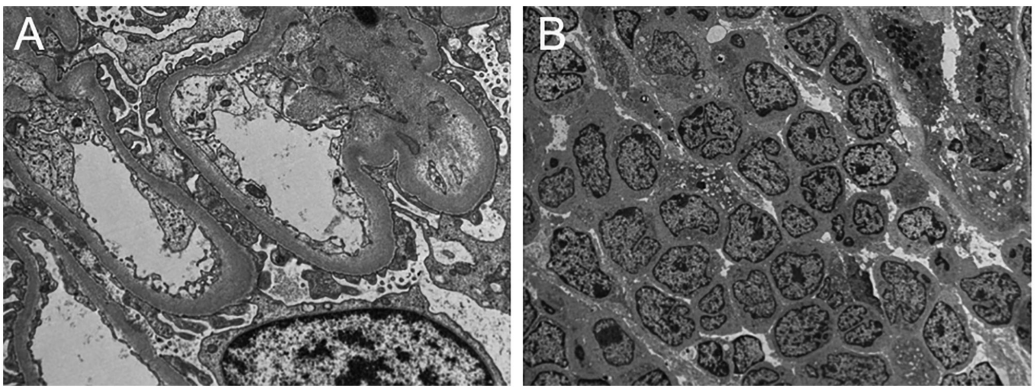

Figure 1. Electron microscopy. Electron microscopy revealed a small amount of renal tissue and a large number of lymphocytes that were morphologically uniform, immature and densely distributed (A) magnification, x4,000; (B) magnification, x1,000.

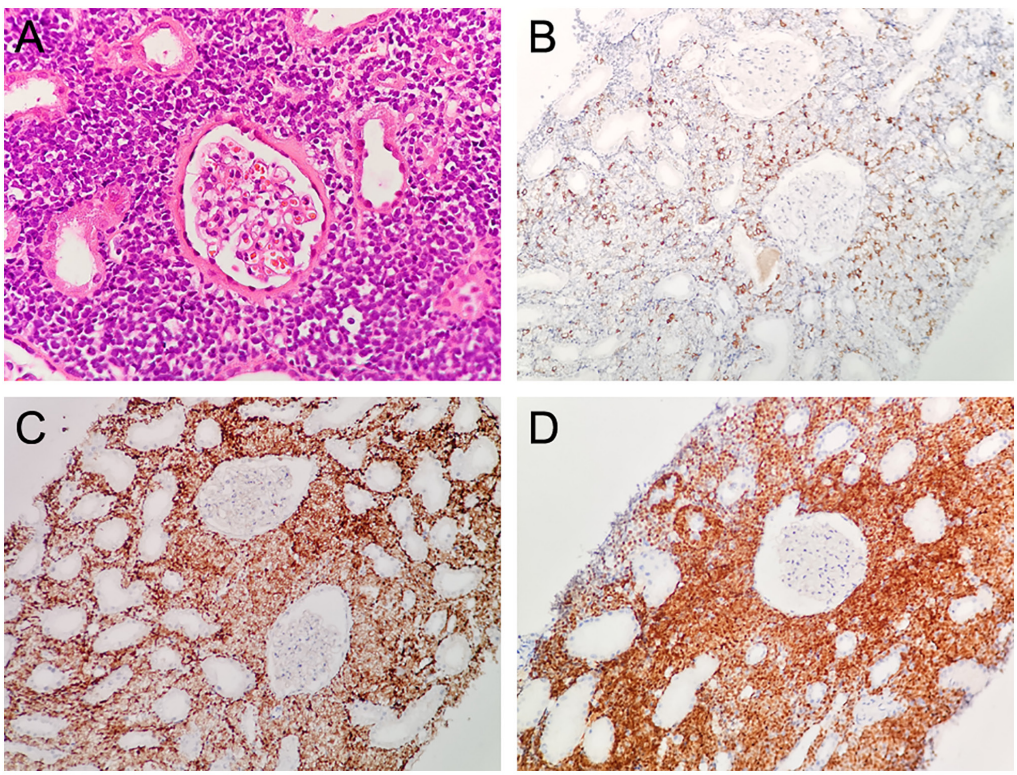

Figure 2. Renal biopsy pathohistological findings. (A) Hematoxylin-eosin staining, magnification, x200. Immunohistochemical staining of (B) CD20, (C) PAX5 and (D) TdT, magnification, x200. CD, cluster of differentiation; Pax, paired box protein; TdT, terminal deoxynucleotidyl transferase.

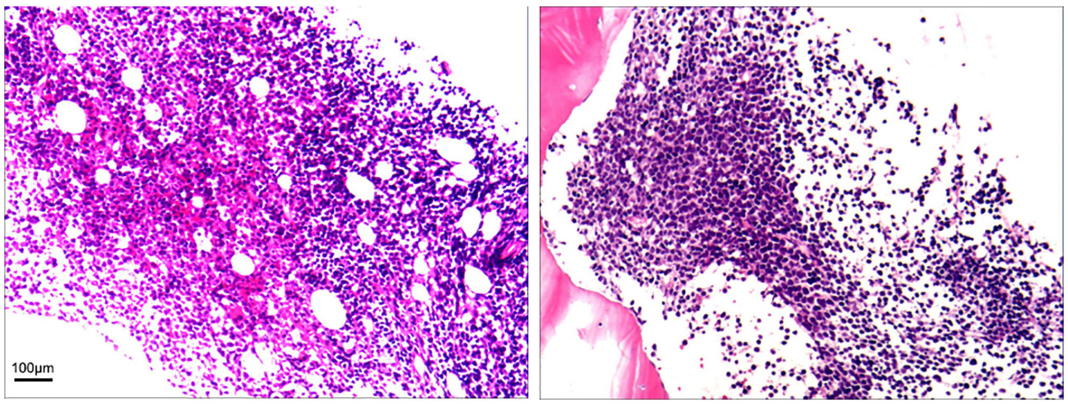

Figure 3. Bone marrow pathohistological findings. Bone marrow aspiration indicated an extremely high level of myeloproliferation and diffuse, patchy cell proliferation (magnification, x100).

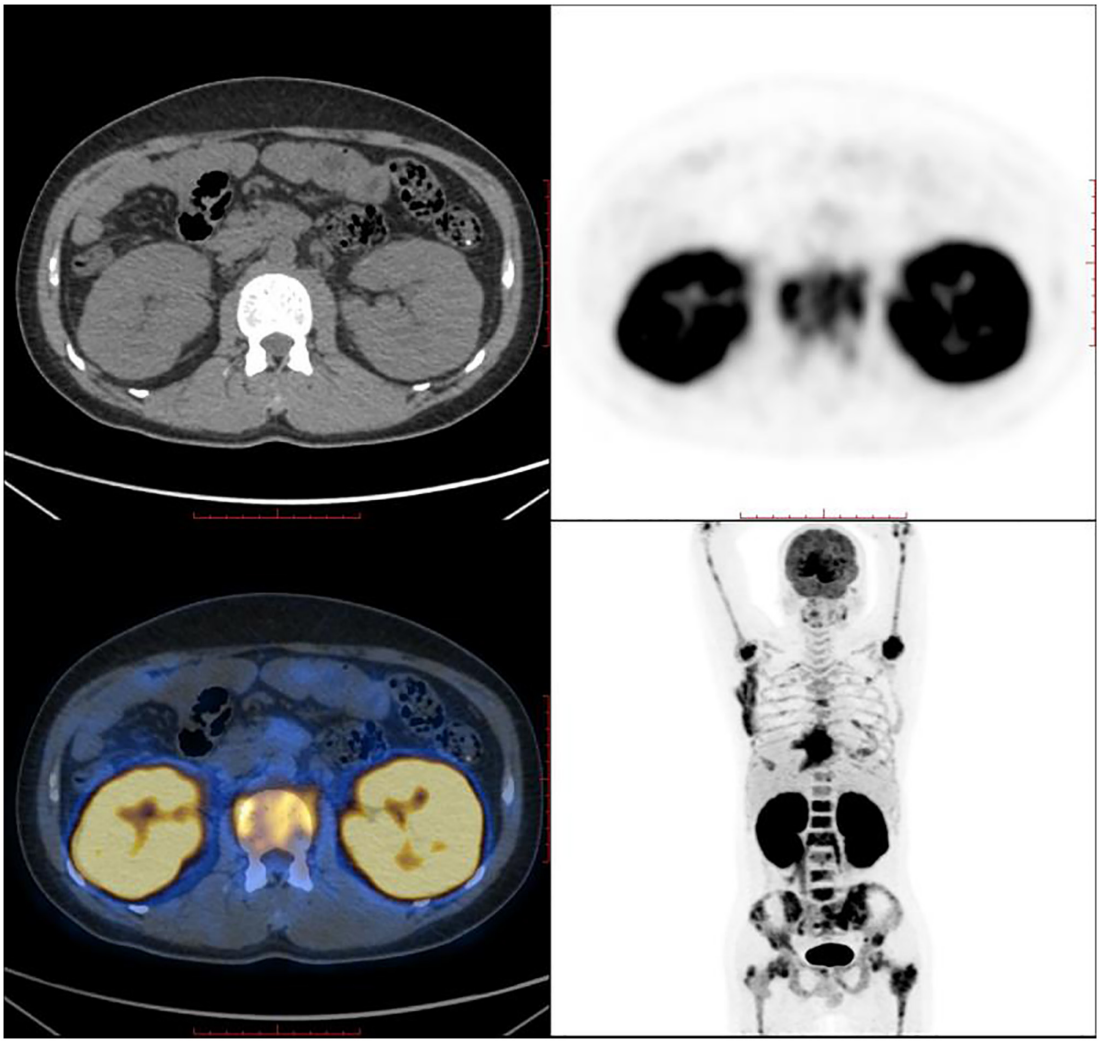

Figure 4. 18F-FDG PET-CT findings. 18F-FDG PET-CT revealed bilateral diffuse renal enlargement with increased metabolism and extensive, localized increased bone metabolism throughout the body. 18F-FDG, 18F-fluorodeoxyglucose; PET-CT, positron emission tomography-computed tomography.

The main acute B-cell lymphoproliferative disease is B-ALL (80%), followed by B-LBL (10%) and mixed B-ALL/B-LBL (10%) (7). The World Health Organization classification groups B-ALL and B-LBL together as B-lymphoblastic leukemia/lymphoma (B-ALL/LBL) (8). B-LBL is a type of rare and highly invasive NHL and accounts for ~10% of LBLs, which in turn account for ~2% of NHLs (9). B-LBL often involves lymph nodes and extranodal locations, such as the skin, bones, and soft tissues. However, renal involvement is rare in B-LBL (7). A literature search identified <5 such

cases in China and elsewhere, including two cases reported in China, one of which was primary renal B-LBL (8,10).

Many factors are associated with renal failure in lymphoma patients, including acute tumor lysis syndrome (11) and urinary obstruction (1); of these, urinary obstruction accounts for ~10% of renal failure. Renal insufficiency is rarely caused by lymphoma-associated bilateral diffuse renal infiltration, which may occur in the renal interstitium or glomerular microcirculation. Lymphoma with glomerular infiltration is a diverse manifestation of renal malignant intravascular lymphoma (12), whereas lymphoma with interstitial infiltration is more common in cases of diffuse large B-cell lymphoma (13). The pathological mechanism of acute renal failure in lymphoma with interstitial infiltration is unclear. A study reported that dense lymphoma-related interstitial infiltration compresses tubules and interstitial capillaries, resulting in lobular obstruction and elevated postglomerular vascular resistance (14).

The cyclophosphamide, doxorubicin, vincristine, and prednisone (CHOP) regimen is the standard chemotherapy scheme for invasive NHL (15). A 2003 multicenter trial in patients with invasive NHL demonstrated that in addition to CHOP, the monoclonal anti-CD20 antibody rituximab was associated with a high survival rate (16). A study also found that early diagnosis and chemotherapy, including rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisolone (R-CHOP), may improve renal function after 2-4 weeks of treatment and may improve 5-year survival (17). Therefore, renal involvement is important to detect, and the addition of rituximab to the standard chemotherapy regimen may improve progression-free survival and overall survival (18,19). When the disease progresses to lymphoma cell leukemia, the treatment scheme for acute lymphocytic leukemia can be adopted, and Hyper-CVAD is a commonly used regimen for adults with newly diagnosed acute lymphoblastic leukemia (20).

In the present study, renal damage was the primary initial symptom. Active prediagnostic use of glucocorticoids rapidly improved renal function; however, with disease progression, hematological involvement occurred, with typical leukemia symptoms. Unfortunately, the patient declined chemotherapy. We wanted to share this case because this lymphoma patient presented with acute renal failure with bilateral renal enlargement as initial symptoms and because this pathologic type is rare, and it is hoped to provide valuable information about lymphoma-associated renal damage and help improve the understanding of this disease.

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Availability of data and materials

The datasets used and/or analyzed during the current study are available from the corresponding author upon reasonable request.

Authors' contributions

JD provided relevant medical records. YJ, GD, DY, and JD participated in the patient's diagnosis and treatment process. YJ drafted the manuscript. JD revised the manuscript. YJ and JD confirm the authenticity of all the raw data. All authors read and approved the final manuscript.

Ethics approval and consent to participate

The present study was carried out in accordance with the code of Ethics of the World Medical Association (Declaration of Helsinki) for experiments involving humans. It was reviewed and approved by the ethics committee of Renmin Hospital of Wuhan University (Wuhan, China; approval no. WDRY2021-KS015).

Patient consent for publication

The patient and his brother provided written informed consent for publication of the medical data and images for this case.

Competing interests

The authors declare that they have no competing interests.

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