Renomegaly and Acute Kidney Injury as Primary Manifestations of Non-Hodgkin's Lymphoma: A Report of Three Cases

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Case Report

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Abstract

Background: In adults with non-Hodgkin's lymphoma, renal enlargement and acute kidney injury occur infrequently at first presentation, especially in T lymphocytic lymphomas.

Case presentation: We report three cases of non-Hodgkin's lymphoma with acute renal injury and bilateral renal enlargement. At diagnosis, one patient presented with an adrenal mass, one patient's lymph node biopsy was consistent with a renal biopsy, and one patient had primary renal lymphoma with no extrarenal disease. Assessment of renal pathology in Case 2 and Case 3 showed interstitial lymphocyte infiltration; the pathological types were non-Hodgkin's diffuse large B lymphoma originating from activated B cells outside germinal centers and non-Hodgkin's T-lymphoblastic lymphoma/leukemia, respectively. Case 1 did not receive anti-lymphoma therapy and died from infection and multiple organ failure within 1 month of hospitalization. Case 2 received eight courses of R-CHOP; her lymphoma recurred 2 years after diagnosis and she died from severe pulmonary infection 3 years after diagnosis. Case 3 received hyper-CVAD regularly and achieved stable renal function; this patient remains under follow-up.

Conclusions: Renal lymphoma may have diverse manifestations, especially primary renal lymphoma without extrarenal involvement. Nephrologists should pay careful attention to these manifestations to ensure accurate diagnosis.

Background

Renal involvement in non-Hodgkin's lymphoma (NHL) is relatively common. Previous studies have suggested that up to 10% of patients with NHL and lymphocytic leukemia may develop kidney injury¹. Lymphoma is associated with various forms of renal involvement, including primary renal lymphoma, other lymphomas involving the kidney, and secondary renal injury caused by therapeutic drugs and tumor lysis. The complexity of distinguishing primary and secondary renal involvement increases the difficulty of diagnosis². Therefore, in clinical practice, diagnosis of renal involvement in lymphoma is challenging for nephrologists.

Acute renal injury (AKI) is common in patients with NHL and lymphocytic leukemia, but it is less common in patients with acute renal injury who initially present in nephrology departments³. Here, we report three cases of NHL with renomegaly and acute renal injury as the primary manifestations of disease.

Report Of Cases

Case 1

In June 2015, a 57-year-old woman presented with abdominal pain for 20 days and anuria for 3 days. Increasing creatine levels within 1 month indicated AKI and was treated by urgent dialysis in the emergency department. The patient had a 10-year history of type 2 diabetes (treated with acarbose) as

well as a 2-year history of depression (treated with paroxetine and olanzapine). The patient had no history of hypertension. Her blood pressure (BP) was 140/80 mmHg and her heart rate (HR) was 110 beats per minute (bpm). Cardiopulmonary and abdominal examinations showed normal results. The results of laboratory examinations are shown in Table 1. Abdominal ultrasound showed intrahepatic patchy hypoechoic area and splenomegaly. Both kidneys were enlarged with echo enhancement: the left kidney was 15.8×7.0×8.2 cm in size and the right kidney was 16.3×7.8×8.5 cm in size. Multiple hypoechoic areas were observed in both kidneys. A 6.3×2.6 cm hypoechoic nodule in the right adrenal region had clear boundaries and dotted blood flow signals indicating the presence of a tumor. An abdominal computed tomography (CT) scan showed that the right adrenal mass and invaded the right liver. In addition, multiple nodules in both kidneys with retroperitoneal lymphadenopathy and splenomegaly were considered to represent lymphoma with multiple metastases. Puncture biopsy of the right adrenal mass was performed under ultrasound. Large numbers of lymphocytes had infiltrated into the tissue of the right adrenal gland tumor the infiltrating cells were medium or large, round, had oval nuclei, and were slightly irregular in shape. Immunohistochemistry showed that the neoplastic lymphoid cells were positive for leukocyte common antigen (LCA), B-cell lymphoma 2 (Bcl-2), CD21, CD20 (diffuse), Bcl-6, melanoma ubiquitous mutated protein 1 (Mum-1), melanoma antigen recognized by T cells 1 (Mart-1), and Ki-67 (>70%) but negative for inhibin, S-100, CD5, CD10, transcription initiation factor 1 (TIF-1), CD3, glypican 3 (GPC-3), and chromogranin A (CgA). The patient was diagnosed with non-Hodgkin's diffuse large B lymphoma of extra-central origin and renal biopsy was not performed because of the poor general condition of the patient and increasing bleeding risk. After renal replacement therapy and supportive therapy, the patient's renal function gradually recovered (urine volume increased to 1500 mL/day and creatinine level gradually decrease to 180 μmol/L). Unfortunately, because of systemic lymphoma metastasis and poor general condition, the patient was unable to receive anti-tumor treatment and died from infection and multiple organ failure within 1 month of hospitalization.

Table 1. Results of laboratory analyses for three cases of non-Hodgkin's lymphoma.

	case1	case2	case3
Age(year)/sex	57/F	48/F	32/M
serum albumin (g/L)	25	30	46.1
serum creatinine (μmol/L)	1097	419	541.2
urea nitrogen (mmol/L)	22.52	11.23	22.99
Uric Acid (μmol/L)	666	548	1962.6
serum potassium (mmol/L)	6.85	4.18	6.12
PTH (pg/ml)	NA	121.7	265.2
WBC (*10 ⁹ /L)	8.69	4.5	6.42
Hemoglobin (g/L)	131	81	113
Platelet (*10 ⁹ /L)	173	132	156
Urine protein	1+	2+	-

Abbreviations: PTH, parathyroid hormone; WBC, white blood cell.

Case 2

A 48-year-old woman presented with abdominal pain and AKI. The patient had a history of appendectomy (30 years previously) and two caesarean sections (17 and 25 years ago). She had no history of hypertension, diabetes, or other chronic diseases. Her BP was 170/95 mmHg and her HR was 110 bpm. Physical examination showed a pale appearance, tenderness in the right upper quadrant, and percussion tenderness over the kidney region. Cardiopulmonary examinations were normal. The results of laboratory examinations are shown in Table 1. Renal ultrasound showed bilateral renal enlargement with echo enhancement; the right kidney was 15.3×6.4 cm in size and the left kidney was 15.1×6.8 cm in size. An abdominal CT scan revealed significantly bilateral enlargement of the kidneys, multiple perinephric lymph nodes, and small retroperitoneal lymph nodes. Bone marrow biopsy findings were unremarkable. Kidney pathology showed massive and monomorphic interstitial infiltration of lymphocytes that were morphologically indistinguishable (Fig.1A).

Immunohistochemical staining was positive for CD20, Bcl-6, Mum-1, and Ki-67 (>50%) (Fig. 1B–E) but negative for CD3, CD10, CD21, and creatinine kinase (CK) (Fig 1F–I). The patient was diagnosed with non-Hodgkin's diffuse large B lymphoma originating from activated B cells outside of germinal centers. Left axillary lymph node pathology showed diffuse proliferation of atypical lymphocytes in the lymph nodes; the infiltrating cells were of medium size with irregular nuclei (Fig. 2A).

Immunohistochemical staining was positive for CD3 (staining of a small number of cells), CD5 (weakly positive), CD20, Bcl-2, Mum-1, and Ki-67 (>50%) (Fig 2B–G), and negative for CD10, CD21, CD23, and

Cyclin D1 (Fig 2H–K), consistent with the kidney pathology findings. After admission, the patient received supportive therapy including antihypertensive agents, sodium polystyrene sulfonate, febuxostat, and diuretics. Following diagnosis with non-Hodgkin's diffuse large B lymphoma originating from activated B cells outside of germinal centers the patient received eight courses of rituximab, cyclophosphamide, hydroxydaunorubicin, oncovin, and prednisone (R-CHOP). Her serum creatine decreased to 156 $\mu\text{mol/L}$ after anti-lymphoma therapy. Her lymphoma recurred 2 years after diagnosis and she was sequentially treated with cyclophosphamide, vincristine, and prednisone (COP) and dexamethasone, ifosfamide, cisplatin, and etoposide (DICE) for 1 year. The patient died from severe pulmonary infection 3 years after diagnosis.

Case 3

A 32-year-old man presented as an outpatient with AKI. His urine was cloudy without changes in urine volume and urinalysis was normal. The patient had no prior medical history. On physical examination, slight enlargement of cervical lymph nodes and bilateral ureter tenderness were observed. Cardiopulmonary examinations were normal. The results of laboratory examinations are shown in Table 1. An abdominal CT scan revealed symmetrical bilateral enlargement of the kidneys (Fig. 3).

Kidney ultrasound showed bilateral enlargement of the kidneys (right kidney 13.6×5.0 cm, left kidney 14.0×5.6 cm) with enhanced echo and bilateral renal calculi. The patient received sodium polystyrene sulfonate, febuxostat, and fluid infusions. His serum creatine and urea levels normalized after supportive therapy. The results of bone marrow biopsy and cervical lymph node biopsy were normal. Although the patient was responding well to treatment, renal biopsy was performed because of unexplained hyperuricemia. The patient was diagnosed with non-Hodgkin's T-lymphoblastic lymphoma/leukemia based on renal pathology. Analysis of kidney pathology showed massive interstitial infiltration of lymphocytes, which were similar in morphology to those of Case 2. Immunohistochemical staining was positive for CD3, CD5, terminal deoxynucleotide transferase (TdT), CD10, CD38, LIM domain only protein 2 (LMO2) (weakly positive), Bcl-2 (weakly positive), and Ki-67 (80%) but negative for CD20, paired box protein 5 (PAX-5), and myeloperoxidase (MPO) (Fig. 4).

The patient received hyper-CVAD (cyclophosphamide, vincristine, adriamycin, and dexamethasone) regularly and maintained stable renal function. A recent abdominal CT scan revealed multiple solid nodules in both kidneys, which we considered to represent lymphoma (Fig. 3)

Discussion And Conclusions

The incidence of renal infiltration in NHL is more than 50%¹. Previous reports suggested that the clinical manifestations of renal involvement of lymphoma can be diverse. Renal involvement is often associated with hematological abnormalities, lymphadenopathy, and solid tumors of organs, which are easily diagnosed by tissue biopsy⁴. However, primary NHL of the kidney is very rare, accounting for only 0.7% to 1.0% of exonerative lymphoma⁵, and more frequent involvements include single (10%–20%) or multifocal

nodules (60%), renal invasion from contiguous retroperitoneal disease (25%–30%), diffuse infiltration (20%), or perirenal involvement (10%)⁶. Notably, patients with kidney involvement without abnormalities of other systems are often difficult to diagnose. Lymphoma-associated AKI can include direct tumor invasion, obstructive nephropathy, ischemic nephropathy caused by tumor compression, immune mediated renal injury⁷, renal injury caused by tumor metabolism (tumor lysis syndrome), and treatment-related renal injury⁸.

The three patients reported here presented to the nephrology department with AKI and bilateral renal enlargement as the first manifestations of disease. Findings were suggestive of lymphomatous infiltration of the kidneys⁹. However, the clinical manifestations and diagnostic results of the three patients were diverse.

The mechanism of AKI in Case 1 was obscure because of the patient's poor general condition and the absence of pathological evidence in the kidney. Both Case 2 and Case 3 underwent renal biopsy, which showed diffuse interstitial infiltration of the kidney by lymphoma cells. However, the mechanisms of AKI in these two cases were quite different. In Case 2, we inferred that the cause of AKI was direct damage to the kidney caused by diffuse lymphoma cell infiltration because levels of uric acid were not significantly increased, there were no signs of urinary tract obstruction, and renal function did not recover after supportive treatment and only gradually recovered after chemotherapy. In Case 3, AKI may have resulted from tumor lysis syndrome and direct injury associated with primary renal lymphoma. However, the renal function of Case 3 returned to normal prior to chemotherapy following symptomatic treatment to lower uric acid levels and achieve rehydration. This suggested that AKI was caused by spontaneous tumor lysis syndrome in this patient. The incidence of spontaneous tumor lysis syndrome in patients with T-lymphoblastic lymphoma is higher than that of other lymphomas¹⁰⁻¹².

For renal involvement associated with solid tumors, enhanced CT is the preferred diagnostic method¹³. The three cases reported here had common renal radiographic features including bilateral renal enlargement. However, enhanced CT should be used with caution in the diagnosis of renal lymphoma because it may not sensitively detect loss of renal function and kidney-infiltrating lesions, and may result in additional kidney damage by contrast agents. Magnetic resonance imaging can prevent contrast agent kidney damage, but may still not be able to distinguish renal infiltration of lymphoma from collecting duct or medullary carcinoma of the kidneys, transitional cell carcinoma, or severe pyelonephritis¹⁴. In AKI without renal replacement therapy (Case 2) and lymphoma with renal invasion (Case 3), imaging is often not sensitive. Especially for patients with negative lymph node and bone marrow biopsies, renal biopsy offers enhanced sensitivity for diagnosis of lymphoma in its early stages^{15, 16}. Therefore, we believe that for patients with AKI, bilateral symmetric renal enlargement, or unexplained hyperuricemia, renal biopsy should be performed as soon as possible even if renal function has already recovered. In addition, when infiltration of the renal interstitium by homogeneous lymphocytes is observed, nephrologists should consider the possibility of lymphoma.

The treatment and prognosis of NHL are closely related to the underlying pathological type. Non-Hodgkin's diffuse large B lymphoma accounts for about one-third of all NHLs and is the most common histologic subtype. R-CHOP is the standard treatment for patients with diffuse large cell lymphoma. The prognosis of patients with diffuse large cell lymphoma is usually assessed using the International Prognostic Index (IPI)¹⁷. According to the IPI, age of more than 60 years, elevated serum lactate dehydrogenase levels, advanced disease, and poor performance status are negative prognostic factors¹⁸. Case 2 was diagnosed with non-Hodgkin's diffuse large B lymphoma originating from activated B cells outside the germinal center and received eight courses of R-CHOP, followed by COP and DICE after recurrence. The IPI score of Case 2 suggested a poor prognosis. T-cell lymphoblastic lymphoma is an aggressive malignancy caused by precursor T cells that occurs primarily in adolescents and young adults and accounts for approximately 2% of all patients with NHL¹⁹. To our knowledge, this report describes the first case of adult renal T-cell lymphoblastic lymphoma with AKI and hyperuricemia as the primary manifestations without extrarenal involvement. Case 3 was diagnosed with non-Hodgkin's T-lymphoblastic lymphoma/leukemia and received hyper-CVAD, which is widely used in the treatment of lymphoblastic lymphoma²⁰. According to previous reports^{21, 22}, the prognosis of lymphoma with renal infiltration is poor. Commonly used prognostic factors, such clinical examination, imaging findings, and specific molecular biomarkers, have not shown consistent performance. Prognostic factors need to be further explored²³.

In conclusion, the three cases described here highlighted the diversity of renal involvement in lymphoma. Renal infiltration of lymphoma should be considered in patients presenting with AKI and nephromegaly, and kidney biopsy should be performed to enable early diagnosis and treatment. Renal lymphoma is common, but its manifestations and mechanisms can vary significantly. Based on the three cases described here, clinicians should consider the possibility of interstitial infiltration of renal lymphoma. The complexity of diagnosis poses a challenge to nephrologists, and accurate diagnosis requires multidisciplinary collaborations.

Abbreviations

NHL: non-Hodgkin's lymphoma

AKI: acute renal injury

PTH: parathyroid hormone

WBC: white blood cell

CT: computed tomography

IPI: international prognostic index

T-LBL: T-cell lymphoblastic lymphoma

Declarations

Ethics approval and consent to participate

Ethical approval was obtained from the Ethics Committee of the Beijing Friendship Hospital, Capital Medical University, China, in accordance with the ethical guidelines of the 1975 Declaration of Helsinki (2021-P2-236-01). And consent exemption was obtained since this was a retrospective case report, informed consent was difficult to obtain, and the patient's sensitive personal information was not included.

Availability of data and materials

All data generated or analysed during this study are included in this published article.

Competing interests

The authors declare that they have no competing interests.

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Authors' contributions

Conceptualization: Sha Liu and Wenhui Liu. Supervision: Zongli Diao, Wang Guo. Pathologic analysis: Yuanyuan Zheng, Qidong Zhang. Writing – original draft: Yu Bai. Writing – review & editing: Sha Liu and Qun Jiang. The author(s) read and approved the final manuscript.

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Figures

Figure 1

Kidney pathology of Case 2. (A) Kidney pathology showed a massive interstitial infiltration of lymphocytes (hematoxylin and eosin). (B-E) Immunohistochemical stains were positive for (B) CD20, (C) BCL-6, (D) Mum-1, (E) Ki-67 (×50%), and negative for (F) CD3, (G) CD10, (H) CD21, (I) CK.(Original magnification×200)

Figure 2

Left axillary lymph node pathology of Case 2. (A) There was diffuse proliferation of atypical lymphocytes in the lymph nodes, and the cells were of medium size with irregular nuclei (hematoxylin and eosin). (B-G) Immunohistochemical stains were positive for (B) CD3 (positive for a small number of cells), (C) CD5 (weakly positive), (D) CD20, (E) BCL-2, (F) MUM-1, (G) Ki-67 (≈50%), and negative for (H) CD10, (I) CD21, (J) CD23, (K) Cyclin D1. (Original magnification×200)

Figure 3

Abdominal computed tomography of Case 3. (A) August 2020, (B) November 2020, (C) January 2021, (D) January 2021 (enhanced).

Figure 4

Kidney pathology of Case 3. (A) Kidney pathology shows a massive interstitial infiltration (hematoxylin and eosin). (B-I) Immunohistochemical stains were positive for (B) CD3, (C) CD5, (D) TDT, (E) CD10, (F) CD38, (G) LMO2 (weakly positive), (H) BCL-2 (weakly positive), (I) Ki-67 (80%) and negative for (J) CD20, (K) PAX-5, (L) MPO. (Original magnification $\times 200$)