CASE REPORT

Diffuse large B-cell lymphoma presenting as bilateral renal infiltration leading to acute kidney injury

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Abstract Acute kidney injury (AKI) because of bilateral renal infiltration is an uncommon presentation of diffuse large B-cell lymphoma (DLBCL). A 52-year-old man presented to our institution with AKI and complaints of fatigue. Ultrasonography revealed a large, 15 cm granulomatous mass arising from the bilateral kidneys. The mass was biopsied laparoscopically, and histopathological analysis revealed evidence of DLBCL. The patient subsequently underwent R-CHOP therapy (rituximab,

cyclophosphamide, doxorubicin, vincristine, and prednisone). Chemotherapy resulted in a rapid decrease in mass size and improvement in kidney function. However, after five courses of R-CHOP, relapse was observed in the central nervous system, and the patient died 220 days after the initial onset of AKI. Post-mortem analysis of renal tissue confirmed the initial diagnosis of DLBCL-associated renal infiltration. To our knowledge, this is the first report of DLBCL presenting as bilateral renal infiltration and AKI.

Keywords Diffuse large B-cell lymphoma · Acute kidney injury · Kidney infiltration · Central nervous system relapse

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Introduction

Malignant lymphoma (ML) can develop in any extra-lymphatic organ. Renal injury is a common and well-characterized complication of lymphoma [1]. In general, lymphoma-induced renal injury occurs because of disseminated renal infiltration, mechanical compression by the tumor, glomerular and tubular damage induced by tumor-associated proteins, and tumor lysis syndrome during chemotherapy treatment [2, 3]. However, infiltration of the bilateral kidneys is rare [4]. Given that there is no lymph tissue within the renal interstitium, the origin of ML cells confined to the kidneys is unknown [2, 3].

Here, we report a case of acute kidney injury (AKI) because of diffuse large B-cell lymphoma (DLBCL) infiltration of the bilateral kidneys, diagnosed by renal biopsy. The diagnosis was confirmed by three separate renal biopsies (at the time of diagnosis, after chemotherapy, and during autopsy).

Case

A 52-year-old man presented to our hospital with weight gain, anuria, and fatigue. Laboratory tests revealed severe kidney injury (Table 1). Of significance, the past medical history of the patient showed the occurrence of gastric cancer, and he had been followed annually with laboratory testing and computed tomography (CT). His renal function was normal at 1 year prior to presentation. Ultrasonography (US), CT, and magnetic resonance imaging (MRI) demonstrated notably enlarged kidneys (Fig. 1a–c). Malignant lymphoma was suspected as the cause of both AKI and kidney enlargement. Fludeoxyglucose-positron emission tomography revealed significant uptake in the bilateral kidneys and interior pelvis (Fig. 1d). To avoid the risk of excessive bleeding because of needle puncture, renal biopsy was performed laparoscopically. Histopathologic analysis of the sample showed massive, diffuse interstitial infiltration with large atypical lymphocytes positive for CD20, CD79a, CD10, and multiple myeloma oncogene 1, and bcl-6-positive B cells. Glomeruli were grossly normal (Fig. 2a). Based on these findings, the patient was diagnosed with DLBCL, and began R-CHOP chemotherapy (rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone) shortly thereafter. Tumor lysis syndrome occurred upon the initial R-CHOP therapy. For this reason, the patient underwent treatment with continuous hemodiafiltration at the intensive care unit. He required dialysis for 1 month. After initiation of R-CHOP, his kidney size normalized on US (Fig. 3a–d), his blood tests improved (lactate dehydrogenase and soluble interleukin-2 receptor value), and maintenance dialysis eventually became unnecessary (Fig. 4). A renal needle biopsy was performed after five courses of R-CHOP, demonstrating resolution of tubulointerstitial lesions and regeneration of renal tubules (Fig. 2b). However, on day 141, the patient was noted to be unsteady on his feet, prompting a brain MRI that revealed multiple brain metastases (Fig. 5a). He underwent radiation therapy and high-dose cytarabine therapy (Fig. 4). On day 191, new disseminated brain and spinal cord lesions were observed on MRI (Fig. 5b). These disseminated lesions enlarged rapidly, leading to elevated central nervous system (CNS) pressure on day 214 (Fig. 5c). The patient died 220 days after the initial onset of AKI. His kidney size

Table 1 Blood analysis and urinalysis on admission

Urine
Specific gravity, 1.010
pH 6.0
Protein (2+)
Sugar (–)
Occult blood (1+)
Urine protein, 0.61 g/gCr
Blood
Leukocyte count, $9060 \times /\mu\text{L}$
Erythrocyte count, $369 \times 10^4/\mu\text{L}$
Hemoglobin, 10.4 g/dL
Hematocrit, 31.0%
Platelet count, $23.4 \times 10^4/\text{L}$
Urea nitrogen, 52.4 mg/dL
Cre, 9.01 mg/dL
eGFR, 5.63 ml/min/1.73 m ²
Uric acid, 13.9 mg/dL
Total protein, 6.5 g/dL
Albumin, 3.5 g/dL
Sodium, 139 mEq/L
Potassium, 5.0 mEq/L
Chloride, 107 mEq/L
Corrected serum calcium, 2.41 mmol/L
Phosphate, 3.5 mmol/L
Lactate dehydrogenase, 2790 IU/L
C-reactive protein, 6.67 mg/dL
Creatine kinase, 193 U/L
PR3-ANCA, <1.3 U/mL (normal <3.5)
MPO-ANCA, <1.3 U/mL (normal <3.5)
IgG, 862 mg/dL
IgG4, 18 mg/dL
IgA, 155 mg/dL
IgM, 110 mg/dL
Soluble interleukin-2 receptor, 2605 U/mL (normal 145–519)
Thymidine kinase, 1200 U/L
CEA, 2.0 ng/mL
CA19-9, 6 U/mL
Venous blood gas (room air)
pH, 7.362
PCO ₂ , 3.76 kPa (28.2 mmHg)
HCO ₃ [–] , 15.6 mmol/L
Anion gap, 22 mEq/L
Tissue of bone marrow normal tissue component

Fig. 1 **a** Ultrasound image demonstrating bilateral renal enlargement. Left kidney size: 15.0×7.7 cm, right kidney size: 14.8×8.7 cm. **b** Contrast-enhanced computed tomography (CT) image demonstrating bilateral renal enlargement and granulomatous infiltration. **c** Magnetic resonance imaging (MRI) of the kidneys

demonstrating low signal and multiple nodules (T_2 -weighted image). **d** Fludeoxyglucose-positron emission tomography demonstrating increased standardized uptake values (standardized uptake value: SUV max 16.1)

Fig. 2 **a** Periodic acid-Schiff (PAS) stain of the first renal biopsy, obtained upon the initial diagnosis. The renal interstitium demonstrated massive, diffuse infiltration with large, atypical lymphocytes, whereas the glomeruli were largely normal in appearance

(magnification $\times 200$). Scale bar 100 μ m. **b** PAS stain of the second renal biopsy, obtained after five courses of R-CHOP therapy. The tubulointerstitial lesions resolved, and renal tubules regenerated (magnification $\times 200$). Scale bar 100 μ m

Fig. 3 Renal ultrasound (US) following chemotherapy, demonstrating normalization of kidney size. **a** US image on admission. Left kidney size: 15.0×7.7 cm, right kidney size: 14.8×8.7 cm. **b** US image at day 29 (after one course of R-CHOP). Left kidney size: 11.3×6.2 cm, right kidney size: 11.3×5.2 cm. **c** US image at day

55 (after two courses of R-CHOP). Left kidney size: 10.1×4.9 cm, right kidney size: 10.0×4.5 cm. **d** US image at day 125 (after five courses of R-CHOP). Left kidney size: 10.4×5.2 cm, right kidney size: 9.5×5.1 cm

normalized (Fig. 6a). Post-mortem examination of the kidneys confirmed inflammatory cell infiltration of the tubulointerstitial regions of the kidney, consisting mainly of small lymphocytes (Fig. 6d). Multiple brain metastases were observed in the cerebrum and cerebellum, consisting of large (Fig. 6b, c), CD20-positive lymphocytes (Fig. 6e, f). Brain metastases were surrounded by areas of bleeding and necrosis (Fig. 6b, c).

Discussion

Approximately one-third of patients with DLBCL present with renal infiltration on autopsy [4, 5], although bilateral renal involvement is uncommon. Therefore, AKI because of diffuse, bilateral tubulointerstitial infiltration is a rare initial presentation of lymphoma [6]. The most common effects of renal infiltration in patients with

DLBCL include direct effects such as obstruction, infiltration, and rupture of the urinary tract; indirect effects such as hypercalcemia, paraproteinemia, amyloidosis, and glomerulonephritis; treatment-related effects such as radiation fibrosis, uric acid/xanthine/oxypurinol precipitation or stones; and other effects including sepsis, volume depletion, and autoimmune diseases [7].

In the present case, the initial renal biopsy showed normal glomeruli and diffuse infiltration of lymphoma cells within the renal interstitium. Several normal tubular structures were also observed. Based on these results, we postulated that renal tubules became dysfunctional, leading to a state of ‘atubular glomeruli’ that resulted in abolition of the nephron units, and AKI [8]. Lymphoma cells directly obstruct, infiltrate, or cause rupture of whole sites of the urinary tubule. It is thought that infiltrated lymphoma cells cause glomerular collapse [9].

Fig. 4 Rapid decrease of serum lactate dehydrogenase (LDH) and soluble interleukin-2 receptor (sIL-2R) following initiation of chemotherapy (five courses of R-CHOP: 65 mg rituximab, 1300 mg cyclophosphamide, 70 mg doxorubicin, 2 mg vincristine, and 100 mg prednisone). He was treated by radiation therapy from days 146 to 189 (whole-brain radiation: total 37.8 Gy; localized radiation: total 17.4 Gy). Renal biopsy was performed at day 12 and day 126 before

and after R-CHOP therapy. We injected cytarabine (Ara-C)/dexamethasone (DEXA) into the spinal column at day 190. High-dose Ara-C therapy was performed from days 202 to 204. We actively treated the patient, but he died on day 220. HD hemodialysis, CHDF continuous hemodiafiltration, RB renal biopsy, Cr creatinine, LDH lactate dehydrogenase, sIL-2R soluble interleukin-2 receptor, UV urinary volume

There is no lymph tissue within the renal interstitium; hence, the origin of ML cells confined to the kidneys is unknown. Bilateral primary renal lymphoma is often associated with AKI, and patients generally survive for less than 1 year [2, 3]. In many cases, infiltration of lymphoma cells into the kidney is confirmed on post-mortem autopsy. However, in our patient, a definitive diagnosis was made on ante-mortem biopsy. In addition, the therapeutic effect of R-CHOP therapy was observed on a second renal biopsy, and relapse was confirmed on autopsy.

Renal involvement in malignant lymphoma is often a sign of progressive disease [10]. The frequency of renal lesions as extranodal involvement in ML is relatively high in autopsy cases. However, it is difficult to diagnose it before the death of the patient, because renal symptoms, as the initial symptoms, are extremely rare in ML [4]. Patients with non-Hodgkin's lymphoma with renal involvement show rapid improvement in renal function and tumor size with treatment. However, treatment failure is common, as in the present case [11]. DLBCL with renal involvement at

Fig. 5 **a** Magnetic resonance imaging (MRI) showing central nervous system (CNS) metastases in the septum lucidum and ependymophalon on day 141 (yellow arrows). **b** MRI demonstrating a new lesion in the lobus temporalis, and growth of the lesion in the

ependymophalon. Disseminated lesions were observed in the L1–4 spinal cord on day 191 (yellow arrows). **c** CNS lesions leading to brainstem compression on day 214 (yellow arrows)

the time of diagnosis is associated with a particularly poor prognosis, in part because of the high incidence of CNS involvement [11]. Although the mechanism of dissemination of lymphoma into the CNS remains unclear, the expression of certain genes and adhesion molecules on the surface of non-Hodgkin's lymphoma cells has been associated with a tendency towards extranodal involvement, tumor aggressiveness, and poorer outcomes [11, 12]. Current strategies to prevent CNS relapse in patients with renal involvement, including the use of rituximab, are generally ineffective. A previous report demonstrated that renal involvement is an independent risk factor for CNS relapse in patients with DLBCL in both the pre- and post-rituximab treatment eras [13].

Renal infiltration of DLBCL is considered a secondary process, and is thought to be a feature of progressive disease. Given the association of renal involvement with CNS

relapse, the early evaluation of the CNS, for example with spinal fluid testing, is important in this patient population.

Conclusion

Herein, we reported a patient with AKI because of DLBCL infiltration of the bilateral kidneys. Although tumor size and renal function rapidly improved with R-CHOP therapy, the patient ultimately died from CNS relapse. The kidneys were serially biopsied (at the time of diagnosis, following R-CHOP chemotherapy, and during autopsy). Serial biopsies allowed us to make the initial diagnosis, document improvement after chemotherapy, and identify renal recurrence after CNS relapse. We believe that this is the first report of three serial renal biopsies performed in a patient with DLBCL presenting with AKI.

Fig. 6 **a** Appearance of the bilateral kidneys (macro autopsy). His kidney size normalized. **b** Appearance of the cerebrum (macro autopsy). Massive metastatic lesions were found in the brain parenchyma. Lesions of metastases were surrounded by areas of bleeding and necrosis (*yellow arrows*). **c** Appearance of the cerebellum (macro autopsy). The cerebellum was characterized by the same findings as the cerebrum. **d** Renal specimens obtained during autopsy demonstrating partial tubular and tubulointerstitial fibrosis and mild tubule-interstitial infiltration with CD20-negative lymphocytes. No

residual DLBCL was observed [hematoxylin–eosin (HE) stain, magnification $\times 200$]. **e** Specimens of the cerebrum and cerebellum obtained during autopsy demonstrating multiple sites of hemorrhagic necrosis surrounding areas of metastasis [hematoxylin and eosin stain, magnification $\times 40$ (large windows) and $\times 400$ (small windows)]. **f** Specimens obtained during autopsy demonstrating diffuse CD20-positive lymphocyte infiltration. CD20 stain, magnification $\times 40$ (large windows) and $\times 400$ (small windows)

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Author contributions All authors treated the patient, and made decisions regarding the patient’s examinations and therapies. TO reviewed the previous publications and drafted the manuscript. SH, MS, SD, and TM supervised the generation of the manuscript. TO and YK were principal physicians of the patient, and treated him on both an inpatient and outpatient basis. All authors contributed to the interpretation of the disease etiology and discussion. All authors have read and approved the final manuscript.

Compliance with ethical standards

Conflict of interest The authors declare that there are no conflicts of interest.

Human and animal rights This article does not contain studies with human or animal participants.

Informed consent None.

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