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Exceptional Case

Acute kidney injury in the setting of AIDS, bland urine sediment, minimal proteinuria and normal-sized kidneys: a presentation of renal lymphoma

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Abstract

Acute kidney injury in HIV patients is primarily related to HIV-mediated viral or immunological disease or to treatment-related toxicity (tenofovir). Neoplasms are a rare cause of non-obstructive acute kidney injury, primarily because when they occur, they manifest as discrete masses and not as diffuse infiltration of the renal parenchyma. Diffusely infiltrating tumors include carcinoma of the renal pelvis invading the renal parenchyma, renal lymphoma, squamous cell carcinoma (from lung) metastasizing to the kidney and infiltrating sarcomatous type of renal cell carcinoma. To be classified as a true case of renal lymphoma, the tumor should have escaped detection on routine imaging preceding biopsy, and lymphoma-associated renal failure/nephrotic proteinuria should have given rise to the indication for kidney biopsy. We present here a case of an acute kidney injury due to renal lymphoma in a patient with acquired immune deficiency syndrome that manifested clinically as bland urine sediment, minimal proteinuria and normal-sized kidneys. Chemotherapy resulted in complete reversal of acute kidney injury.

Keywords: acute kidney injury; HIV; renal lymphoma

Clinical history and initial laboratory data

A 49-year-old Caucasian male with past medical history of acquired immunodeficiency syndrome (AIDS) presented with generalized weakness, diarrhea and vomiting. The patient was on anti-retroviral therapy, and his most recent CD4 count was 150 and viral load undetectable. Social history was significant for frequent cocaine and marijuana use for the past 1.5 years in addition to his long-standing history of narcotic use (LSD, crystal meth and ecstasy). His home medications included Bactrim, Prilosec and Atripla (tenofovir, efavirenz and emtricitabine).

On examination, the patient was afebrile, pulse 70 beats/min, blood pressure 150/80 mmHg (no orthostatic change), and respiratory rate 14 breaths/min. Auscultation of the heart and lungs was normal. The abdomen was soft, nontender and without any organomegaly. There was no peripheral edema, cyanosis, lymphadenopathy or clubbing.

Initial laboratory results (SI units; reference range) revealed a white blood cell count (WBC) of 6.1 × 10^3/μL (6.1 × 10^9/L; reference range 4.5–10.8 × 10^3/μL) with normal differential; haemoglobin, 11 g/dL (110 g/dL; reference range 13.5–17.5 g/dL); platelets, 449 × 10^3/μL (449 × 10^9/L; reference range 150–450 K/μL); potassium, 5.3 mEq/L (5.3 mmol/L; reference range 3.5–5.1 mEq/L); blood urea nitrogen, 66 mg/dL (23.6 mmol/L; reference range 9–20 mg/dL); serum creatinine, 3.6 mg/dL (318.2 μmol/L; reference range 0.6–1.2 mg/dL); bicarbonate, 17 mEq/L (17 mmol/L; reference range 22–30 mEq/L); serum calcium, 9.3 mg/dL (2.3 mmol/L; reference range 8.4–10.3 mg/dL); and serum albumin, 3.4 g/dL (34 g/L; reference range 3.5–5.0 g/dL). Liver function tests revealed aspartate transaminase of 52 U/L (52 U/L; reference range 15–46 U/L), alanine aminotransferase of 80 U/L (80 U/L; reference range 13–69 U/L), alkaline phosphatase of 766 U/L (766 U/L; reference range 38–126 U/L), and total bilirubin of 0.3 mg/dL (5.1 μmol/L; reference range 0.2–1.3 mg/dL).

He had normal renal function, as measured by a normal creatinine 4 months prior to admission. Evaluation of the acute kidney injury showed no pre-renal component as his FENA was 1.8%, and he had no glucose, ketones or nitrites in his urine. Trace protein was reported on urine dipstick with 240 mg of protein per gram of creatinine on a random urine specimen. Microscopically,

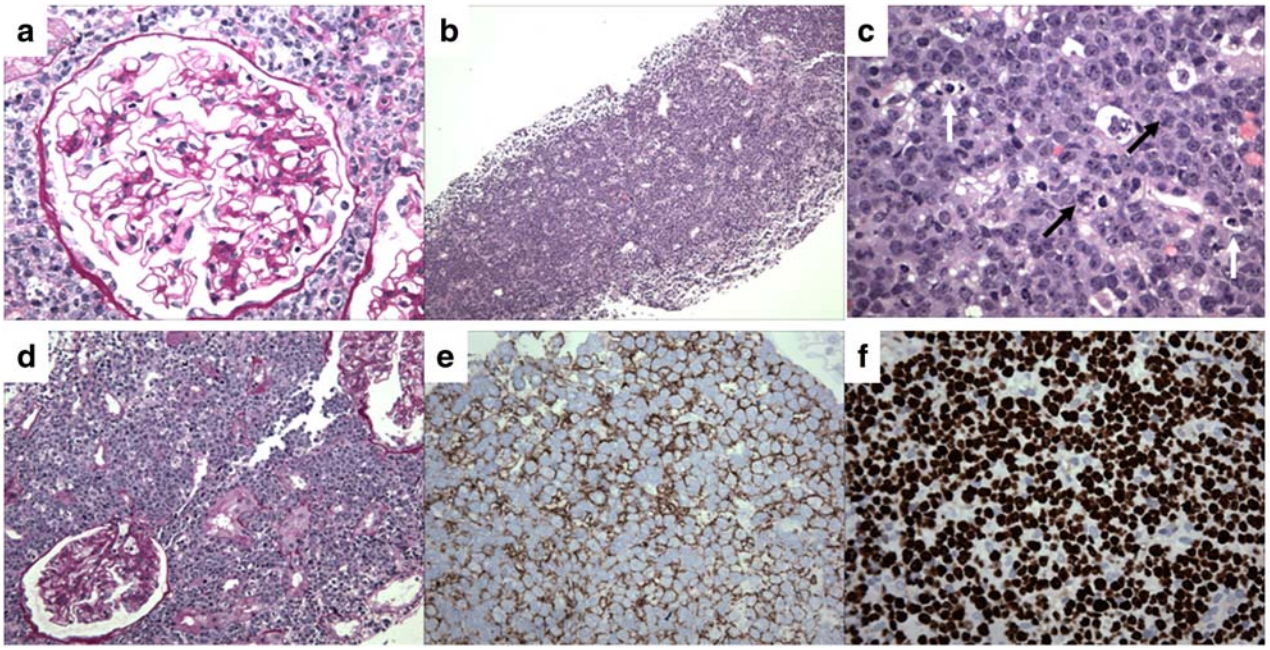

Fig. 1. Renal biopsy. Glomeruli appeared normal in size and cellularity with patent capillary lumina (**a**). The renal cortex was diffusely infiltrated by sheets of lymphoid cells (**b**) which were enlarged and showed frequent mitosis and apoptosis (**c**; black arrows point to mitotic figures, and the white arrows point to apoptotic bodies). The sheets of infiltrating cells diffusely expanded the interstitium, separating and compressing the tubules (**d**). There was no evidence of uric acid deposits in the tubules. The large lymphoid cells were positive for B-cell marker—CD20 (**e**). In addition, the large B lymphoid cells expressed Ki-67 protein (a cellular marker for proliferation) as depicted in (**f**).

the urine sediment contained only occasional tubular epithelial cells and no casts. Renal ultrasound showed normal-sized kidneys (right, 13.1 cm; left, 13.2 cm) with no evidence of hydronephrosis, perinephric collections, calcifications or masses. Computerized scan of the abdomen was also suggestive of normal-sized kidneys with no hydronephrosis.

The serological work-up was essentially normal. Complement C3 level was 131 mg/dL (131 g/L; reference range 90.00–180.00 mg/dL), and complement C4 level 27.70 mg/dL (27.7 g/L; reference range 10.00–40.00 mg/dL). Anti-neutrophil cytoplasmic antibody (ANCA P and C) and anti-nuclear antibody (ANA) were negative, rheumatoid factor level was normal, and serum and urine immunofixation revealed no M-band. Serum hepatitis B surface antigen and hepatitis C virus antibody were negative. Stool wet mount was negative for cryptosporidium cysts, parasites and *Clostridium difficile*.

In summary, the patient had acute non-oliguric (1500 mL/24 h.) kidney injury, of unclear etiology. The patient was treated with intravenous fluids. Repeat urine microscopy remained unchanged. Over the next 3 days, the urine output decreased, renal function deteriorated to a peak creatinine of 6.9 mg/dL (607 μmol/L; reference range 0.6–1.2 mg/dL) and the patient developed signs of uraemia; haemodialysis (HD) was initiated, and a percutaneous kidney biopsy was performed.

Kidney biopsy

A CT-guided renal percutaneous biopsy of the lower pole region was done.

Microscopic description. Sections were stained with haematoxylin and eosin (H&E), periodic acid–Schiff (PAS), trichrome and Jones metanamine silver (JMS). There were nine glomeruli present in the specimen; none of which was segmentally or globally sclerotic. Glomeruli appeared normal in size and cellularity with patent capillary lumina (Figure 1A). The renal cortex was diffusely infiltrated by sheets of lymphoid cells which were enlarged and showed frequent mitosis and apoptosis (Figure 1B and C). The sheets of infiltrating cells diffusely expanded the interstitium, separating and compressing the tubules (Figure 1D). There was no evidence of uric acid deposits in the tubules. The atypical lymphoid population was positive for CD20 and CD79a (B-cell markers) and showed a >90% proliferation index with the Ki-67 stain (Figure 1E–F).

Immunofluorescence. Standard immunofluorescence studies showed no evidence of glomerular disease of the immune complex type or dysproteinaemia-related renal disease.

Bone marrow and molecular studies

Bone marrow analysis revealed lymphoma cells. The cells had characteristic cytoplasmic vacuoles thus suggestive of Burkitt lymphoma (Figure 2A). Immunohistochemical stains showed positivity for CD20 (B-cell marker) and CD10 (germinal center marker), and CD 3 (T-cell marker) was negative (Figure 2B–D). Molecular studies with fluorescence *in situ* hybridization (FISH) demonstrated rearrangement involving MYC (8q24) in 52% of the cells and were negative for clonal rearrangement involving BCL6. The findings were thus characteristic of Burkitt lymphoma.

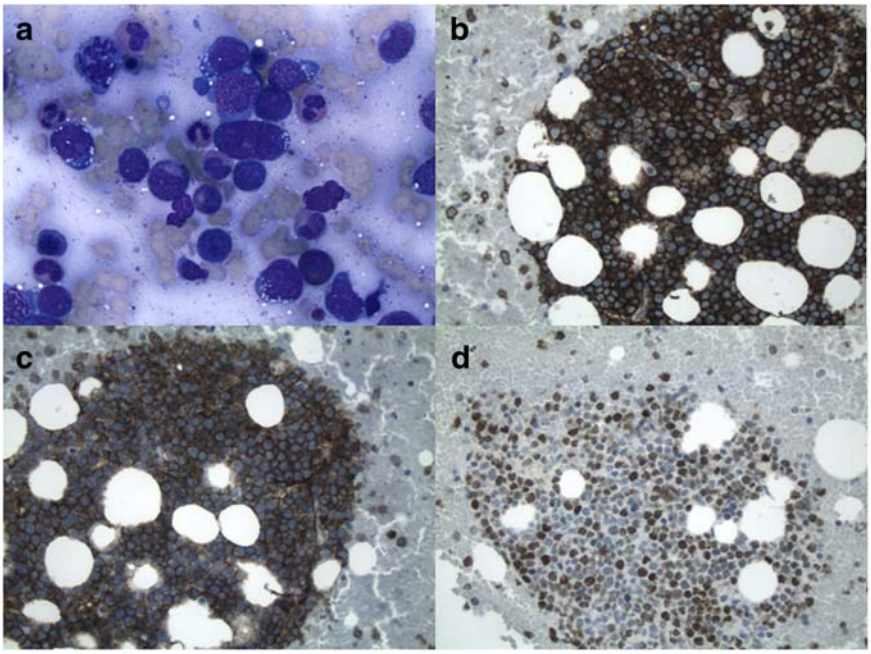

Fig. 2. Bone marrow aspirate suggestive of Burkitt cells (vacuoles in the cytoplasm—**a**). Immunohistochemical stains showed positivity for CD20 (B-cell marker—**b**), CD10 (germinal centre marker—**c**) and BCL6 (germinal centre marker), while CD 3 (T-cell marker—**d**) was negative. Molecular studies with FISH demonstrated rearrangement involving MYC (8q24) in 52% of the cells and were negative for clonal rearrangement involving BCL6. The findings were thus characteristic of Burkitt lymphoma. These immunohistochemical stains thus supported the diagnosis of Burkitt lymphoma.

Diagnosis: Burkitt lymphoma with diffuse infiltration of the kidneys (HIV infection-associated)

Patient was begun on chemotherapy, and haemodialysis (HD) was continued. Three weeks after the initiation of chemotherapy, his renal function showed signs of improvement. At present, the patient is off HD, and his creatinine has stabilized at 0.9 mg/dL.

Discussion

Though most renal neoplasms manifest as discrete masses on imaging, some may diffusely infiltrate the kidney and may not be diagnosed with conventional imaging. Diffusely infiltrating tumors include carcinoma of the renal pelvis (transitional cell and squamous cell carcinoma) invading the renal parenchyma, renal lymphoma, squamous cell carcinoma (from lung) metastasizing to the kidney and infiltrating sarcomatous type of renal cell carcinoma [1].

To be classified as a typical case of renal lymphoma, the lymphoma should have gone unnoticed on conventional imaging (due to diffuse infiltration of the kidney), and the lymphoma should be the primary cause of renal failure (e.g. lymphoma-associated renal failure and lymphoma-associated proteinuria) [2]. This entity therefore does not include those cases where the tumor presented as a discrete kidney mass, thus warranting further investigation of a suspected tumor.

Renal lymphoma is commonly a diffuse large-cell lymphoma and is predominantly of B-cell lineage (non-Hodgkin's lymphoma) with T-cell immunophenotype seen in only a few cases [3]. Based on renal biopsy, renal lymphomas can be of two broad histological patterns—interstitial or intra-glomerular. These varieties have distinct presentation and histological characteristics. Of the 60 cases reported in English literature so far, the former pattern was noted in 80% of the cases, and the latter in only 20%. One recent report suggested that intra-glomerular lymphoma may transform into a diffuse type also infiltrating extra-glomerular structures [4]. Apart from the usual presenting symptoms of acute renal failure, like generalized weakness, nausea (depending on the BUN) and anorexia, the patient may have night sweats, back pain and weight loss. However, the patient may be asymptomatic with only laboratory values suggestive of acute kidney injury. Moreover, due to the rarity of the disease, lymphoma as the primary diagnosis of an underlying renal failure is rare. Of the reported 60 cases in English literature, renal lymphoma was in the differential diagnosis in only 16% of the cases prior to the kidney biopsy [2]. The salient features of the two histological patterns are listed in Table 1.

Our patient had an interstitial renal lymphoma (IRL). Patients usually present with acute renal failure, with minimal proteinuria, bland urine sediment and bilateral enlargement

Table 1. Salient features of the two histological patterns of renal lymphomas: interstitial renal lymphoma (IRL) and intra-glomerular lymphoma (IGRL) [2]

	Interstitial type	Intra-glomerular type
Incidence	80% of cases	20% of the cases
Acute renal failure	87%	45%
Proteinuria	Minimal (never nephrotic)	50% have nephrotic
Kidneys enlarged	91%	Only in 10%
Extra-renal involvement	52%	36%

of the kidneys on imaging. Our patient's kidney size was at the upper limit of normal (~13 cm each). Depending on the degree of tumor infiltration, the interstitium may be expanded leading to separation and compression of the tubules, as was the case in our patient. The dense interstitial infiltrate of monomorphic lymphoid cells is the primary cause of renal failure as it leads to increased intra-renal pressure, tubular compression and increased peri-tubular capillary pressure, and therefore also decreases in the GFR [5]. The glomeruli are normal, and the tubules are devoid of any injury to the epithelial cells.

The intra-glomerular renal lymphoma (IGRL) was seen in only 20% of the cases reported so far. It is also called malignant intravascular lymphomatosis or angiotropic large-cell lymphoma [6]. Patients usually present with nephrotic-range proteinuria, normal-sized kidneys, and a milder renal failure as compared with the IRL type. The latter is primary because the infiltration is limited to the glomeruli and therefore the intra-renal pressure is not elevated. The likely mechanism for nephrotic-range proteinuria in patients with intra-glomerular lymphoma is probably related to the local release of permeability-enhancing cytokines by the lymphoma cells [7].

The histological differential diagnoses for IRL include interstitial nephritis and diffuse infiltrative lymphocytosis syndrome, whereas IGRL is more likely to be confused with endocapillary proliferative glomerulonephritis [8]. In both IRL and IGRL, the atypical appearance of the infiltrate should prompt an immunohistochemical work-up that would reveal the true lymphomatous nature of the process [4].

The treatment of acute renal failure in patients with renal lymphoma is chemotherapy. While re-reviewing the data collected from previous reported cases by Törnroth *et al.*, it becomes evident that in patients with IRL, ~84% of the patients showed recovery of renal function after successful chemotherapy, whereas only 54% of the patients with IGRL achieved similar results. Furthermore, post-recovery, nephrotic-range proteinuria continued to persist in half of the IGRL cases. Unfortunately, renal recovery may not always manifest into better long-term survival. Of the reported deaths in patients with IRL type of lymphoma, 24 of the 44 patients died within an average of 7.8 months (range 1–52 months) post-diagnosis. In the remaining patients, long-term survival follow-up is not available in subsequent literature. A similar calculation of mortality for the IGRL patients would be less appropriate as the number of patients is very limited (only six) [2].

Take-home message

Diffuse bilateral renal lymphoma should be considered in the differential diagnosis of acute renal failure in an HIV patient with inconclusive bland urine sediment and normal/enlarged-sized kidneys with or without nephrotic-range proteinuria. Elevated LDH and uric acid may further increase clinical suspicion for lymphoma. Percutaneous kidney biopsy provides the most expedient means of establishing the diagnosis. Prompt initiation of chemotherapy should lead to improvement in renal function, but renal recovery may not always manifest into better long-term survival.

Conflict of interest statement. None declared.

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