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CASE REPORT

Non-Hodgkin's Lymphoma Primarily Presenting with Fanconi Syndrome and Acute Kidney Injury

Wen-ling Ye^{1*}, Bing Han², Bing-yan Liu¹, Chan Meng¹, Wei Ye¹,
Yu-bing Wen¹, Hang Li¹, and Xue-mei Li¹

¹Department of Medicine, ²Department of Hematology, Peking Union Medical
College Hospital, Chinese Academy of Medical Sciences &
Peking Union Medical College, Beijing 100730, China

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KIDNEY involvement is common in non-Hodgkin's lymphoma (NHL) with incidence up to 30%-40% in autopsy studies.¹ However, it usually occurs late in the course of the disease and is clinically silent. Clinically overt renal disease including acute kidney injury (AKI) as its primary manifestation is rarely reported, moreover, Fanconi syndrome (FS) is extremely rare as the main manifestation in NHL. In this report, we presented a case of NHL primarily presenting with FS and AKI due to diffuse interstitial infiltration of NHL cells and emphasized the important role of renal biopsy, especially renal immunohistochemical analysis in the diagnosis of renal diffuse lymphoma.

CASE DESCRIPTION

A 48-year-old woman was admitted in February 2007 with nausea and vomiting for 9 months. In an examination in October 2006, laboratory tests showed that hemoglobin was 80-100 g/L, serum potassium 2.82 mmol/L, Cl^- 110 meq/L, HCO_3^- 17 mmol/L, and serum creatinine (SCr) 117 $\mu\text{mol/L}$ with normal gastroscopy and enteroscopy findings.

Because of continued nausea and weakness, she was transferred to our hospital for further examination and treatment after general supporting treatment. During the past 9 months, she lost 20 kg in body weight. She had no history of Sjögren's syndrome and medicine allergy. Physical examination found appearance of anemia. No body surface lymphadenopathy or hepatosplenomegaly, no abnormal lung and heart findings, and no edema was observed. The laboratory investigations in our hospital showed that SCr was 255 $\mu\text{mol/L}$, blood urea nitrogen 8.52 mmol/L, Cl^- 111 meq/L, lactic dehydrogenase 214 U/L, lactic acid 8.4 mmol/L, and normal glucose. Arterial blood gas analysis revealed severe metabolic acidosis with HCO_3^- being 9.6 mmol/L, bases excess -16 mmol/L, and anion gap 24.6 mmol/L. Renal tubule associated investigation produced the following results: urine glucose 5.5 mmol/L, urine amino acid (+), serum potassium 3.0 mmol/L; hypouricemia with serum uric acid at 138 $\mu\text{mol/L}$; hypophosphatemia with phosphorus at 0.87 mmol/L; and proximal tubular HCO_3^- reabsorption rate 16%. The 24-hour urine measurement showed protein at 1.96 g and potassium 124.32 mmol. Serum immunoglobulin and light chain tests were normal and immunoserologic analysis results including ANA, ds-DNA, ENA, ANCA were all negative. Protein electrophoresis and immune electrophoresis did not find abnormal protein. Ultrasonography showed the

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*Corresponding author Tel: 86-10-65295058, E-mail: wenlye2003@yahoo.com

size of the left kidney was 11.5 cm×5.5 cm×5.5 cm and that of the right kidney 10.8 cm×5.4 cm×5.4 cm without obstruction. CT scan displayed bilateral enlarged kidneys and mildly irregular surface with uniform density, showing no evidence of mass, retroperitoneal lymphadenopathy, or hepatosplenomegaly. Percutaneous renal biopsy revealed nearly normal morphology of glomeruli with negative immunofluorescence staining for IgG, IgA, IgM, C3, C4, and C1q. Most tubules were compressed by diffuse infiltrated lymphoid cells in interstitium (Fig. 1A). Bone marrow smears for three times did not find atypical lymphoid cells.

The patient was given potassium chloride to treat severe hypokalemia, and NaHCO₃ for metabolic acidosis. After administration of prednisone 1 mg·kg⁻¹·d⁻¹, SCr rapidly dropped to normal level after 1 week. However, she still needed a large dose of NaHCO₃ (15-20 g/d) to maintain HCO₃⁻ concentration at the low limit of normal level due to lactic acidosis. Subsequently, immunohistochemical analysis indicated that lymphoid cells infiltrated in the kidneys were strong positive for B-cell antigens CD20 and CD79α and only some were with positive staining of CD3 (Fig. 1B). The final diagnosis was diffuse large B cell lymphoma with AKI (failure in RIFLE criteria) and FS, renal tubular acidosis, and lactic acidosis. Two months later, repeated bone marrow biopsy also showed localized lymphoid cells with strong positive CD20 expression. The patient received the treatment of R-CHOP protocol, including cyclophosphamide, adriamycin, vincristine, and prednisone combined with rituximab. When acidosis was improved three days after chemotherapy, NaHCO₃ was stopped. Unfortunately, she developed severe pneumonia after chemotherapy and died in July 2007.

DISCUSSION

Renal involvement as a part of systemic lymphoma is quite frequent. However, it often appears in the form of

asymptomatic hematuria, proteinuria, or insidious renal failure in most cases. The presentation of complete FS, renal tubular acidosis, and AKI consequent to renal NHL is extremely rare.

The patient in this case initially manifested digestive system symptoms such as nausea, vomiting, and weakness, therefore had been treated and examined with gastroscopy and enteroscopy in the Department of Gastroenterology. The renal lesion was not suspected due to normal SCr level. When transferred to our hospital, she presented with AKI (failure phase according to RIFLE classification), severe hyperchloremic metabolic acidosis, and hypokalemia with renal potassium wasting. Renal tubular investigation displayed glycosuria with normoglycemia, aminoaciduria, proteinuria, hypouricemia, hypophosphatemia, and increased proximal tubular HCO₃⁻ excretion, consistent with FS. FS is a transport defect in the proximal renal tubule leading to renal losses of phosphate, uric acid, bicarbonates as well as glucose, amino acids, and other organic compounds. In adults, it is usually caused by Sjögren's syndrome, light chain deposition disease, amyloidosis, and exposure to heavy metals or other agents, etc. However, FS secondary to NHL is quite rare. After excluding other causes based on clinical and laboratory test results including normal protein and immune electrophoresis, negative ANA and ENA, FS was confirmed to be the result of tubular damage caused by squeezing of diffuse lymphoid cell infiltration in interstitium. Ultrasound and CT showed mildly enlarged kidneys. Tubular and interstitial nephritis was highly suspected according to renal morphologic changes. The patient was administrated with prednisone and responded well with rapid improvement of renal function. However, metabolic acidosis was still quite severe with significantly elevated anion gap and lactic acidosis that could not be explained by interstitial nephritis and tubular dysfunction. Renal immunohistochemical investigation displayed densely infiltrated lymphoid cells with

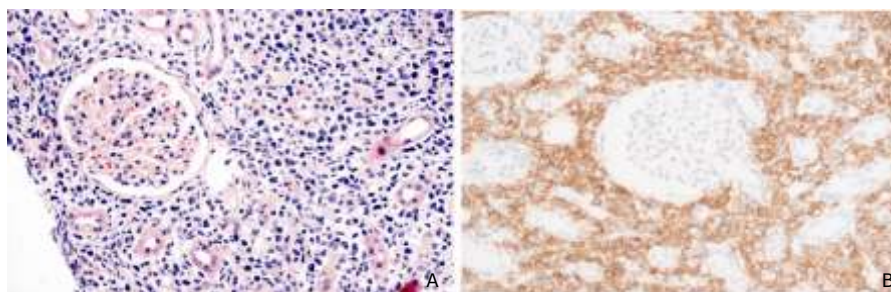


Figure 1. HE staining (A) and immunohistochemical analysis results (B) of kidney biopsy.

- A. Light microscopy revealing diffuse infiltration of lymphoid cells in the interstitium and highly compressed tubules; HE staining ×200
- B. Strong positive expression of B-cell antigen CD20 in the infiltrated cells. DAB ×200

strong expression of B-cell antigen, and renal NHL was ultimately confirmed.

Malignant lymphomas can affect kidneys in several ways. They may precipitate AKI by causing ureteral or renal vascular obstruction, or by paraneoplastic mechanisms such as hypercalcemia and hyperuricemia.²⁻⁵ Furthermore, it has also been reported that lymphoma may occasionally impair renal function by causing glomerulonephritis, including membrane proliferative glomerulonephritis, minimal change disease, focal segmental sclerosis, mesangial proliferative glomerulonephritis, and monoclonal immunoglobulin deposit disease.⁶⁻⁸ Although AKI caused by direct renal parenchymal infiltration has been reported in the literature,⁹⁻¹¹ FS and renal acidosis as the primary manifestation of NHL is rarely seen. Renal tubular dysfunction and AKI in this patient were considered to be due to tubular compression and lesions caused by dense interstitial infiltration according to the pathophysiological characteristics. In addition, the rapid improvement in renal function and acidosis after treatment of NHL with prednisone and R-CHOP provided further evidence that NHL was the cause of her renal dysfunction. Some criteria have been suggested for the diagnosis of primary renal lymphoma, including: (1) renal failure as the initial presentation, (2) enlargement of the kidneys without obstruction, (3) diagnosis made only based on renal biopsy, (4) absence of other causes of renal failure, and (5) rapid improvement of renal function after radiotherapy or systemic chemotherapy.¹² Considering the marked renal lesions and the absence of extra-renal involvement such as lymphadenopathy, hepatosplenomegaly, or bone marrow infiltration at the time of renal biopsy, we postulated that the kidneys in this case were the primary location of NHL.

The prognosis of renal NHL is variable. Early and accurate diagnosis is very important in guiding appropriate treatment. Most of the limited cases reported in the literature showed rapid systemic progression and a poor prognosis with median survival within 9 months after presentation.^{13,14} The addition of rituximab to CHOP protocol may improve the outcome of renal NHL.^{15,16} Besides, AKI caused by diffuse infiltration of tumor cells seemed to have a rapid response to chemotherapy.^{9,10} In this patient, AKI and metabolic acidosis also dramatically improved after treatment with prednisone and R-CHOP.

In conclusion, AKI and FS caused by NHL is rather rare, but lymphoma should be seriously considered in the differential diagnosis of renal tubular dysfunction especially in patients with enlarged kidneys or other unexplained symptoms by renal disease. Renal biopsy serves a crucial role in the diagnosis. In cases of dense interstitial infiltra-

tion, immunohistochemical investigation can define the precise nature of the infiltration, guiding appropriate therapy.

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