Primary renal lymphoma presenting as renal failure: A case report and review of literature from 1989

Lee SB et al. PRL presenting as AKI

Seul-Bi Lee, Young-Min Yoon, Ran Hong

Abstract

BACKGROUND
Primary renal lymphoma (PRL) is extremely rare with an incidence of 0.7% among extranodal lymphomas. Occult renal lymphoma, which mimics medical renal disease and bilateral renal involvement, presents a diagnostic challenge to nephrologists and radiologists as the clinical and radiological findings are mostly non-specific or inconclusive. Acute kidney injury (AKI) is not an uncommon finding in renal infiltration due to malignant lymphoma. However, only 14% of cases are detected before death, and the low diagnostic rate may be due to the non-specific clinical manifestations of renal involvement, with only 0.5% of these cases presenting with AKI. Moreover, PRL is difficult to diagnose based on clinical, biochemical, and radiologic features, especially, in the case of bilateral diffuse involvement.

CASE SUMMARY
Herein, we report a 74-year-old woman with primary diffuse large B-cell lymphoma who presented with AKI diagnosed by ultrasound-guided needle biopsy. We also report the clinicopathologic findings of 121 PRL cases reported since 1989, by conducting a literature review of published cases.
CONCLUSION

A timely renal biopsy provides the most expedient means of establishing the diagnosis. Thus, early identification of the disease by the clinician facilitates early diagnosis toward effective treatment.

Key Words: Lymphoma; Kidney; Acute kidney injury; Case report


Core Tip: We report a patient with bilateral primary renal lymphoma (B-PRL) presenting with acute kidney injury (AKI), and conducted a literature review of 121 cases of PRL since 1989. Among the 121 cases, 29.8% were bilateral. AKI occurred in all bilateral cases, and 71.4% of patients who died were diagnosed with B-PRL. There is a need to discuss more active treatment for B-PRL. In particular, differentiating diffuse involvement of lymphoma from other kidney diseases causing AKI is difficult clinically or radiologically; therefore, a kidney biopsy is essential for the diagnosis. Clinicians should endeavor to make a preoperative diagnosis, to avoid unnecessary surgery.

INTRODUCTION

Primary renal lymphoma (PRL), defined as a lymphoma involving the kidneys in the absence of extrarenal lymphoma, is a rare disease. Additionally, PRL accounts for approximately 0.7% of extranodal lymphomas[1], as the kidney is an extranodal organ and the renal parenchyma does not contain lymphatic tissue[2]. Occasionally, patients present with nonspecific signs and symptoms including flank pain, weight loss, hematuria, a palpable mass, or symptoms of acute kidney injury (AKI). Evaluation of renal lymphoma is important and includes differentiating PRL from other renal neoplasms, making pathologic diagnoses, and preserving renal parenchyma and
function⁹. Radiologically, the typical computed tomography (CT) pattern in renal lymphoma can be grouped approximately as multiple renal masses (approximately 60%, most common), solitary masses (< 6%, rarest), renal invasion from retroperitoneal disease, or diffuse renal infiltration⁰,ⁱ. The diffuse infiltration pattern is always bilateral, observed in approximately 25%-30% of renal lymphomas⁶. Moreover, the pattern is difficult to diagnose by imaging alone due to the non-specific manifestations. In particular, PRL with a diffuse growth pattern in the bilateral kidney may clinically mimic medical renal disease and even escape detection during the routine radiological work-up, including ultrasonography (US) and CT, preceding biopsy. Percutaneous renal biopsy is generally used in the diagnosis of medical renal diseases, although the indications for biopsy vary. Renal neoplasms, which are typical urological disorders, are not generally recommended for percutaneous biopsy⁷, but the tumor may be detected incidentally during a biopsy. For a rapid and confirmative diagnosis, kidney biopsy remains the gold standard. Therefore, although rare, clinicians should consider lymphoma as a differential diagnosis during percutaneous renal biopsy for diagnosing the aforementioned lesions. According to a population-based analysis using the Surveillance, Epidemiology, and End Results Program, factors such as old age, primary diffuse large B-cell lymphoma (DLBCL) histologic type, and male patients are associated with short overall survival (OS)⁸.

To the best of our knowledge, to date, 121 cases of PRL have been reported in the literature⁹,¹²,⁴,⁹,⁹⁷. Herein, we report the case of primary renal DLBCL of 74-year-old woman presenting with AKI, diagnosed by US-guided needle biopsy. We also conducted a literature review of the 121 cases reported since 1989 and described their clinicopathologic findings. This study was approved by the Institutional Review Board (IRB) of Chosun University Hospital, Gwangju, Korea, which waived the requirement for written informed consent due to the nature of the study (IRB No. 2023-02-020).

**CASE PRESENTATION**

**Chief complaints**
A 74-year-old woman who was treated outside our hospital due to complaints of general weakness, hematuria, dysuria, and decreased renal function was transferred to Chosun University Hospital, Gwangju, Korea, as her renal function did not improve despite treatment.

**History of present illness**

Clinically, rapid progressive glomerulonephritis (RPGN) was suspected. Two days after admission, US-guided percutaneous renal biopsy was performed to confirm the pathologic diagnosis, before initiating steroid treatment. Contrary to expectations, the light microscopic examination identified diffuse infiltration of pleomorphic cells throughout the specimen. The pleomorphic cells were immunoreactive for CD20, bcl-2, bcl-6, and MUM-1, but negative for CD3, CD10, and Epstein-Barr encoding region in situ hybridization (Figure 1). No fluorescence deposit was identified during immunofluorescence examination. In electro-microscopic examination, no electron-dense deposit was observed, and the glomerular basement membrane appeared normal in thickness, contour, and texture. However, strikingly, diffuse prominent infiltration of atypical lymphocytes was observed in the interstitium. The cells displayed round to oval cleaved and non-cleaved nuclei with variable clumping of chromatin, and large prominent, margined nucleoli (Figure 1). We diagnosed the condition as DLBCL, not medical renal disease. After pathologic diagnosis, radiologic re-evaluation was performed. Abdominal CT examination (with contrast) revealed diffuse homogeneous enhancement in both kidneys without definite visible cortico-medullary differentiation, and lymphomatous involvement was diagnosed. A few mild enlargements of lymph nodes in the pericardial and paraaortic chains were identified, and such nodes were considered to indicate secondary lymphomatous involvement. On fluorodeoxyglucose-positron emission tomography CT, intense hypermetabolism (19.6) was identified in both kidneys, and some lymph nodes exhibited mild hypermetabolism (Figure 2). In the laboratory tests, serum lactate dehydrogenase (LDH) level was elevated to 376 U/L (125-220 U/L). The international prognostic index (IPI) was reported as 3 when the following
laboratory data and clinicopathologic factors were considered [old age, 1; Eastern Cooperative Oncology Group (ECOG) performance status (PS), 1; Ann Arbor stages III–IV, 0; serum level > 1 × normal, 1; and > 1 extranodal site, 0].

4 History of past illness
The patient had no previous renal problems.

Personal and family history
There was no specific personal or family history.

Physical examination
The patient looked ill.

Laboratory examinations
After admission, the blood urea nitrogen (normal range, 7.0-20.1 mg/dL)/creatinine (0.57-1.11 mg/dL) levels on June 30, July 9, and July 11, 2022 were as follows: 27.7/4.09; 41.0/6.61; and 48/7.62 mg/dL, respectively.

Imaging examinations
Radiologically, renal US exhibited heterogeneously increased parenchymal echogenicity and a 1.43 cm-sized hypoechoic cystic lesion in the right kidney. Thus, the radiologist suggested probable medical renal disease with a right cystic lesion. During abdominal CT (contrast-free CT while admitted to the emergency room), no neoplastic lesion was suspected.

FINAL DIAGNOSIS
The patient was diagnosed with DLBCL.

TREATMENT
She was immediately started on chemotherapy (CTx), which was composed of rituximab-cyclophosphamide, vincristine, adriamycin, and prednisolone.

OUTCOME AND FOLLOW-UP
The patient succumbed to her illness 3 mo after diagnosis during her third round of CTx.

DISCUSSION
As demonstrated during the literature search, according to Stallone et al[1] who reported 29 cases in a literature review in 2000[66,76,98,99], PRL is very rare with an incidence of 0.7% in extranodal lymphomas[1]. Since 1989 when Paganelli et al[2] presented the first patient with PRL diagnosed by open kidney biopsy, to our knowledge, 121 cases have been reported in the medical literature, including our case (Table 1). The present study reviewed all 121 cases of PRL reported in the literature since 1989.

Of these 121 cases, the male-to-female ratio was 1.6:1 (72:45; unknown, 4 patients). The average age of the patients was 55 years, and the distribution is displayed in Table 2. A total of 36 (29.8%), 81 (66.9%), and 4 (3.3%) cases of bilateral renal involvement, unilateral lesion, and unknown, respectively, were observed. The bilateral involvement in PRL may be age-related. Patients aged < 40 years have higher bilateral renal involvement (17/23, 73.9%) compared with those aged ≥ 40 years (19/98, 19.4%) (Table 2).

Histologically, DLBCL is the most common (62/121, 51.2%) lymphoma, followed by marginal zone lymphoma (23/121, 19.0%). Symptoms and signs include abdominal distension, fever, flank pain, nausea and vomiting, hematuria, frequency, urinary retention, hydronephrosis, and AKI. Some cases were identified incidentally without any symptoms. According to Coggin[100], AKI in renal lymphoma may occur by several causes such as infections and obstructive urinary disease with leukemic infiltration contributing to the progression of renal failure. Bridoux et al[101] suggested that invasion of lymphoma to the renal interstitium induces compression of tubules and peritubular
capillaries, which leads to tubular obstruction and increase of post-glomerular vascular resistance.

In the current review, AKI with symptoms was found in 11 cases (8.9% of all the cases and 30.6% of cases with bilateral lesions), and all exhibited bilateral diffuse renal involvement. However, the incidence of AKI did not correlate with age but occurred more consistently in those over 40 years old (< 40 years old, 1/23, 4.3%) (Table 3). Renal lymphoma can present as a solitary mass (10%-25% of cases) or multiple parenchymal nodular masses of variable sizes, typically 1.0 to 4.5 cm in diameter, which is the most common pattern in approximately 50%-60% of cases. The second most common pattern is a retroperitoneal nodular lesion with continuous extension into the kidneys or perinephric space (observed in 25%-30% of cases). Diffuse renal enlargement without distortion of kidney shape or formation of any discrete masses was found in 6%-19% [102]. The unilateral masses and grossly nodular forms are relatively easily detected by US or CT; therefore, when necessary, the patients undergo open renal biopsy or nephrectomy. On the contrary, bilateral diffuse infiltrative lesions are difficult to detect by radiologic examination. Furthermore, due to various symptoms of lymphomatous infiltration, they are often mistaken for medical renal disease, and frequently percutaneous needle biopsy is performed for confirmative diagnosis. In our case, no definite mass-like lesion was identified on abdominal CT due to bilateral diffuse involvement of PRL, and a sono-guided percutaneous needle biopsy was performed to diagnose RPGN, clinically. In this case, based on the clinical and radiological background, renal involvement of malignant lymphoma could not be suspected.

Of all 121 patients, 96 had the following prognostic data: 68 (56.2%) patients survived, 21 (17.4%) died during/before/shortly after treatment, and 5 (4.1%) had relapsed disease. The mortality rate was especially high in patients younger than 10 years of age at 45.5%, and was 30.4% and 14.3% for those aged < 40 and ≥ 40 years, respectively. In addition, when the mortality rate was stratified by the location of the tumor, 41.7% (15/36) of patients demonstrated bilateral involvement whereas 7.2% (6/83) had unilateral lesions. Younger patients and those with bilateral PRL had a shorter survival
time and more rapid disease progression compared to older individuals. Therefore, special procedures should be considered for the patients mentioned above, including a combination of surgery, CTx, or radiotherapy (RTx).

To date, CTx remains the main treatment for PRL. Among these 121 cases, 99 (81.8%) were treated with CTx (CTx alone or in combination), 67 (55.4%) with single CTx, and the remainder received various combination therapies including RTx, surgery, stem cell transplantation, and surgery. Regardless of the treatment, the overall mortality rate was 17.1%. When classified according to the treatment, the mortality rate of patients on single CTx was 21.2% (14/66), whereas, with combined therapy, a much lower mortality rate was observed [surgery with CTx, 12.5% (3/24); no treatment, 1 case; steroid treatment, 1 case; surgery, 1 case; surgery with concurrent chemoradiation therapy and CTx with stem cell transplantation, no death]. Apart from single CTx, the number of patients on other therapies was small; therefore, this result should be interpreted with caution. To date, CTx remains the most-preferred treatment; however, a combination of CTx with RTx, surgery, and other methods should be considered in young patients or those with bilateral PRL.

Using the IPI, 4 independent patient risk groups with any combination of the following five clinical variables were identified, including age, LDH level, tumor stage, ECOG-PS, and extranodal sites of disease[103]. Moreover, the IPI has been widely used in clinical applications and is the standard practical prognostic tool for patients with DLBCL. In our case, the IPI was 3 (old age, 1; ECOG-PS, 1; Ann Arbor stages III-IV, 0; LDH > 1 × normal, 1; and > 1 extranodal site, 0). In addition to the IPI, because the correlation between cancer and inflammation has received attention in recent years, the prognostic significance of platelet/lymphocyte ratio (PLR) and neutrophil/lymphocyte ratio (NLR) in DLBCL has been reported in several studies[104]. For nearly all oncology records, PLR and NLR are calculated and routinely investigated from platelets, lymphocytes, and neutrophil counts. They are easily available measures in daily clinical practice, are inexpensive, and can provide useful prognostic information for the management of DLBCL[104]. Wang et al[104] reported markedly short OS and progression-
free survival in patients with higher NLR and PLR compared with those with low NLR and PLR. Patients with a high NLR exhibit significantly low ECOG-PS, a high disease stage, and B symptoms, more extranodal sites of disease, and high IPI and LDH levels at diagnosis. Patients with a high PLR more frequently displayed significantly low ECOG-PS and B symptoms and a high LDH level at diagnosis. This revealed that patients with a PLR < 150 or NLR < 2.32 at diagnosis experienced better relapse-free survival and OS than those with a PLR ≥ 150 or NLR ≥ 2.32. In their study, NLR displayed no significant difference in multivariate analysis; however, univariate and multivariate analysis confirmed the predictive ability of PLR, indicating that PLR may be superior to NLR as a prognostic factor for DLBCL. In the present case, the pretreatment PLR was 186 (≥ 150) and NLR was 8.23 (≥ 2.32), implying a poor prognosis [platelets, 279000/μL; lymphocytes, 1500/μL; lymphocytes (%), 18.2%; and neutrophils (%), 67.2%].

This literature review had several limitations. Most importantly, all follow-up data were obtained from different article references and therefore have different follow-up periods. Thus, further studies are required regarding the prognosis of the disease.

Pathological diagnosis is important for the early diagnosis of PRL. When PRL shows bilateral and diffuse patterns, as in our case, predicting the diagnosis based on clinical and biochemical characteristics may be difficult, as PRL may clinically mimic refractory medical renal disease. Thus, a kidney biopsy would be required for confirmation of a radiologic or clinically suspected lymphoma. A biopsy is essential following a diagnosis of renal lymphoma, especially PRL, to institute early treatment, to achieve a cure in patients. Additionally, kidney biopsy helps confirm the exact subtype of lymphoma to apply appropriate treatment.

**CONCLUSION**
In conclusion, we report a 74-year-old patient with PRL presenting with AKI, and we conducted a literature review of 121 cases of PRL since 1989, to report their clinicopathologic findings. The literature search demonstrated that bilateral PRL is rare and has a poor prognosis. Among the 121 cases, only 36 were bilateral PRL, similar to our
case. Additionally, AKI occurred in all bilateral PRL cases, and 71.4% of patients who
died were diagnosed with bilateral PRL. Therefore, a need to discuss more active
treatment for bilateral PRL is necessary. Moreover, bilateral renal involvement in
malignant lymphoma can cause AKI. In particular, differentiating diffuse involvement
(rather than the nodular form) clinically or radiologically from other kidney diseases that
cause AKI is difficult; therefore, a kidney biopsy is essential for the diagnosis of renal
lymphoma. Thus, clinicians should endeavor to make a preoperative diagnosis, to avoid
unnecessary surgery.
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