Renal Dysfunction in Patients With Direct Infiltration by B-Cell Lymphoma

Lea Corlu, Nathalie Rioux-Leclercq, Michel Ganard, Olvier Decaux, Roch Houot, Cécile Vigneau

KI REPORTS
KIReports.org
CLINICAL RESEARCH

Renal Dysfunction in Patients With Direct Infiltration by B-Cell Lymphoma

Lea Corlu[1], Nathalie Rioux-Leclercq[2], Michel Ganard[3], Olivier Decaux[4], Roch Houot[3] and Cécile Vigneau[1,2,3,4,5]

[1]CHU de Rennes, Service de Néphrologie, Rennes, France; [2]CHU de Rennes, Service d'Anatomo-cytopathologie, Rennes, France; [3]CHU de Rennes, Service d'Hématologie, Rennes, France; [4]CHU de Rennes, Service de Médecine Interne, Rennes, France; and [5]IRSET, Rennes, France

Background: B-cell lymphoproliferative disorders with renal involvement are relatively frequent, but remain poorly described. A kidney biopsy is usually required to detect the renal lesions that are often missed using other diagnostic tools.

Methods: We retrospectively identified 34 patients with renal lymphoma diagnosed by percutaneous kidney biopsy (PKB) at Rennes University Hospital and its affiliated hospital centers between January 1, 2004, and May 1, 2016. Clinical, biological, radiological, and histological characteristics were collected at biopsy time.

Results: The included patients had Waldenström macroglobulinemia ($n = 12$; 35.3%), chronic lymphocytic leukemia/lymphocytic lymphoma ($n = 10$; 29.5%), high-grade B-cell lymphoma ($n = 6$; 17.6%), and low-grade B-cell lymphoma ($n = 6$; 17.6%). The median follow-up was 29 months. Renal involvement led to renal function impairment in 29 patients (85.3%), among whom 20 had acute kidney injury (70%), and to nephrotic syndrome in 4 patients (11.8%). Only 13 patients (38.2%) presented morphological kidney anomalies among whom 5 showed bilateral infiltration. Histologically, interstitial infiltrate (97.1%) was the most common kidney lesion, and 9 patients (26.5%) had specific lymphomatous intraglomerular lesions. After hematological treatment ($n = 29$), a renal response was observed only in 8 patients (27.6%).

Conclusion: Renal involvement in the context of B-cell lymphoproliferative disorders is not uncommon. PKB is the best method to confirm this diagnosis. It should be performed early to rapidly initiate the hematological treatment to preserve kidney function.

Kidney Int Rep (2019) **4,** 688–697; https://doi.org/10.1016/j.ekir.2019.02.008
KEYWORDS: acute kidney injury; kidney biopsy; renal lymphoma

Differently from renal diseases associated with monoclonal gammopathy, renal impairment in the context of B-cell lymphoproliferative disorders remains poorly described. In patients with such disorders, all areas of the renal parenchyma may be affected through different mechanisms: specific tumor infiltration, obstructive mechanism, tubulopathy related to hypercalcemia, light/heavy-chain deposition disease, direct immuno-chemotherapy toxicity, or lysis syndrome.[1,2] The first reports of renal involvement in B-cell lymphoproliferative disorders mainly concerned patients with chronic lymphocytic leukemia, and underlined the association between lymphomatous infiltration and dysfunction of the affected organ/tissue.[3,4] In 1980, Coggins[2] described the first biopsy-proven case of a patient with lymphoma and renal involvement. Since then, few cases and small series of kidney biopsies showing lymphoma-related kidney lesions have been reported in the literature.[5–8] Recent studies described 48 patients with renal involvement in a large cohort of patients with chronic lymphocytic leukemia and monoclonal B-cell lymphocytosis, and 35 patients with kidney disease associated with monoclonal IgM-secreting B-cell lymphoproliferative disorders or more recently 57 cases of monoclonal gammopathy-related kidney lesions.[9–11] These authors stressed the need of more studies on kidney impairment in B-cell lymphoproliferative disorders. Indeed, kidney involvement in B-cell lymphoproliferative disorders is not uncommon because at autopsy, renal lymphomatous infiltration has been documented in approximately one-third of all patients with lymphoma (mostly B-cell non-Hodgkin lymphoma).[12] However, most of these patients did not have any clinical evidence of renal

Correspondence: Cécile Vigneau, CHU de Rennes, Service de Néphrologie, 2 Rue H Le Guilloux, Rennes, F-35033, France. E-mail: Cecile.vigneau@chu-rennes.fr

Received 21 November 2018; revised 28 January 2019; accepted 4 February 2019; published online 12 February 2019

involvement, and the diagnosis of renal involvement was only done postmortem.[12,13] Primary renal lymphoma without extrarenal involvement is a rare entity and remains controversial,[14,15] particularly because kidneys do not contain lymphatic tissue. On the other hand, kidney involvement could result from secondary hematogenous diffusion in the case of multiorgan involvement or invasion from adjacent retroperitoneal lymph nodes.

Renal impairment complicates the management of these patients and could affect the global prognosis. Its diagnosis in patients with B-cell lymphoproliferative disorders generally requires a kidney biopsy to detect tumor-related lesions that frequently escape other investigations, such as computed tomography (CT) imaging. Therefore, we retrospectively analyzed the clinical, biological, radiological, and histological features of a cohort of patients with B-cell lymphoproliferative disorders and biopsy-proven renal impairment with the aim of finding clinical or laboratory parameters that could predict renal involvement.

PATIENTS AND METHODS

We carried out a retrospective observational study of all patients with B-cell lymphoproliferative disorders who had a PKB at Rennes University Hospital and in the 3 affiliated hospital centers (Saint-Malo, Saint-Brieuc, and Vannes) between January 1, 2004, and May 1, 2016.

Patient Selection

As all kidney biopsies were processed and analyzed in a single reference pathology department in Rennes, we could perform a computerized search using the "lymphoma" code in the central patient database for the selected period. All the files were then reviewed to ensure that they were complying with the 2016 World Health Organization classification of lymphoid neoplasms.[16]

The following information was collected when the patients underwent PKB:

- Clinical data: age, sex, lymphoma type, and staging according to the Ann Arbor classification (modified in Cotswolds),[17] comorbidities (high blood pressure, diabetes, smoking, and dyslipidemia), performance status, history of nephropathy with chronic kidney disease (CKD), systemic symptoms of non-Hodgkin lymphoma (weight loss >10% in 6 months and/or fever >38°C and/or night sweats), presence of lymphadenopathy or extrarenal organ infiltration (hepatomegaly, splenomegaly), symptoms of a possible renal impairment (high blood pressure, flank pain, oliguria or edema), reasons for PKB, and previous corticosteroid therapy.
- Biological data: kidney function assessment: serum creatinine, serum total protein, albuminemia, corrected calcium, urinalysis (particularly, leukocyturia, hematuria, and proteinuria, completed by immunoelectrophoresis if necessary), and immunological tests if indicated (antineutrophil cytoplasmic antibodies, total complement and specific complement proteins, cryoglobulinemia); hematological assessment (complete blood cell count), C-reactive protein, serum lactate dehydrogenase, serum protein immunoelectrophoresis and immunofixation, flow cytometry, bone marrow differential cell count, and bone marrow aspiration and biopsy, if needed.
- Radiological data: kidney ultrasonography, CT, or positron emission tomography–CT imaging.

Histological Examination

After fixation in Bouin's solution, paraffin inclusion, and staining with hematoxylin and eosin, periodic acid-Schiff, methenamine silver–periodic acid-Schiff (Jones' stain), Masson trichrome, and Congo red, kidney biopsies were analyzed by light microscopy. Complementary immunofluorescence analyses were performed with anti-IgG, -IgA, -IgM, -C3, -C4, -C1q, -fibrinogen, -kappa and -lambda light chain antibodies. Lymphomatous infiltration was characterized by immunochemistry, using specific antibodies against CD20, CD23, CD5, CD3, CD10, and cyclin D1. Ultrastructural electron microscopy was performed for 2 samples (2 patients).

Renal and Hematological Responses to Treatment

All available data on hematological and renal treatments were collected (corticosteroids, immunochemotherapy, dialysis) as well as the clinical and laboratory changes. Acute kidney injury (AKI) was defined as an increase of 26.2 μmol/l of serum creatinine in 48 hours, or by a 1.5-fold increase of the baseline serum creatinine value in less than 7 days, which correspond to the stage 1 of the Kidney Disease: Improving Global Outcomes classification.[18]

Definition of Hematological Response

The response to the hematological treatment was classified as partial remission, complete remission (CR), stable disease, or progressive disease, according to the criteria described by Cheson *et al.*[19]

Definition of Renal Response

Serum level creatinine was collected at month 1 (M1), M3, M6, M12, and the latest available follow-up. Renal

Table 1. Patient characteristics

Variable	$n = 34$
Median age, yr	70 [21–88]
Sex ratio, male/female	24/10 (70.9%/29.4%)
Comorbidities[a]	
HBP	17 (50.0)
Diabetes	3 (8.8)
Smoking	12 (35.3)
Dyslipidemia	8 (23.5)
Performance status	
0 or 1	30 (88.2)
> 2	4 (11.8)
Lymphoma	
DLBCL	6 (17.6)
Low-grade NHL	6 (17.6)
CLL/Lymphocytic lymphoma	10 (29.5)
Waldenström macroglobulinemia	12 (35.3)
Median serum creatinine (μmol/l)	215 [61–1504]
Acute kidney injury at diagnosis	20 (58.8)
Serum creatinine >300 μmol/l[b]	10 (50.0)
Serum creatinine > 400 μmol/l[b]	2 (10.0)
Biochemistry	
Albuminemia, g/l	33.6 ± 6.8
serum total protein, g/l	69.7 ± 13.1
Corrected calcium >2.6 mmol/l	4 (11.8)
Potassium >5.5 mmol/l	5 (14.7)
Immunological analysis	
ANCA	0
Complement	17
Consumed[b]	4 (23.5)
Cryoglobulinemia workup	13
Positive[b]	3 (23.1)
Complete blood count	
Cytopenia	25 (73.5)
≥2[b]	6 (24)
Anemia <10 g/dl	17 (50.0)
Hyperlymphocytosis >4 G/l	12 (35.3)
C-reactive protein >10 mg/l	17 (50.0)
Elevated LDH	11 (32.3)
Presence of monoclonal gammopathy	16 (47.1)
Positive blood CMF	18 (52.9)
Bone marrow involvement	30
Positive[b]	24 (80.0)

ANCA, anti-neutrophil cytoplasmic antibodies; CLL, chronic lymphocytic leukemia; CMF, flow cytometry; DLBCL, diffuse large B-cell lymphoma; HBP, high blood pressure; LDH, lactate dehydrogenase; NHL, non-Hodgkin lymphoma.
[a]Comorbidities are not exclusives with a total value higher than 100%.
[b]Percentages are calculated for the subgroups.
Qualitative data: frequency (%). Quantitative data: mean ± SD; median [minimum-maximum].

response was defined as a glomerular filtration rate >60 ml/min estimated using the Modification of Diet in Renal Disease equation, or not worsening of an already present CKD. In patients with nephrotic syndrome (defined as a proteinuria >3 g per 24 hours with albuminemia <30 g/l), partial response was defined as a proteinuria <3 g per 24 hours, and complete response as a proteinuria <1 g per 24 hours. Therefore, patients were classified as renal responders (RRs; complete + partial response) and renal nonresponders.

Statistical Analysis

Categorical variables were compared using the Fisher's exact probability test, and ordinal variables with the Student *t* test. A survival curve with confidence intervals was generated, and comparisons between groups (RRs and renal nonresponders) were performed using the Cox model. *P* values less than 0.05 were considered significant. Statistical analyses were performed with SAS 9.4 (SAS Inc., Cary, NC) and the online tool "BiostaTGV," and with R 3.3.1 for the survival curves.

RESULTS

This study included 34 patients with renal lymphoma diagnosed by PKB between January 1, 2004, and May 1, 2016. Indications for kidney biopsies were as follows: AKI ($n = 14$; 41.2%), significant proteinuria ($n = 7$; 20.6%), nephrotic syndrome ($n = 3$; 8.8%), and CKD with known hemopathy ($n = 2$; 5.9%). In patients with extrarenal involvement, additional biopsies in these other organs were not performed.

Clinical, Biological, and Radiological Findings

The patient's characteristics at PKB are presented in Table 1. Each subtype of B-cell lymphoproliferative disorder was identified, and lymphoplasmacytic lymphoma (i.e., Waldenström macroglobulinemia) and chronic lymphocytic leukemia were the most common (35.3% and 29.5%, respectively). The lymphoproliferative disorder was already known before the biopsy in 21 patients (61.8%), with a median interval of 5 years (0.2–20) between the primary tumor diagnosis and the renal involvement. The diagnosis of lymphoproliferative disorder was made by PKB in 13 patients (38.2%), among whom 5 underwent kidney biopsy for a reason other than suspected lymphoma infiltration. Thirteen patients (38.2%) had CKD higher than stage 3 before the diagnosis of renal lymphoma. Among the clinical features (Tables 1 and 2), general signs of hematological disease were the most common, but some patients reported also symptoms of kidney problems, such as high blood pressure (35.3%), edema (35.3%), oligoanuria (8.8%), and flank pain (2.9%), on average 2.27 months (0–9) before the PKB. No correlation between clinical symptoms and lymphoma type or renal lesions was found. Twenty-nine (85.3%) patients had renal dysfunction: AKI in 20 patients (69%), especially severe AKI in 12 patients (60%) (Table 1). Patients with non-Hodgkin lymphoma had AKI less frequently ($P = 0.053$) (Table 2). The most common urinalysis abnormality was proteinuria (64.7%) mainly mixed proteinuria, whereas leukocyturia was detected in only 8.8% of patients. Only the rate of nonglomerular proteinuria was significantly higher in the group with

Table 2. Comparison according to the lymphoma types

Variable	Whole population ($n = 34$)	Waldenström macroglobulinemia ($n = 12$)	CLL/Lymphocytic Lymphoma ($n = 10$)	Low-grade NHL ($n = 6$)	DLBCL ($n = 6$)	*P*
Renal function impairment						
Yes	29 (85.3)	11 (91.7)	10 (100)	5 (83.3)	3 (50.0)	0.053
With Acute kidney injury[a]	20 (69)	10 (90.9)	6 (60.0)	2 (40.0)	2 (66.7)	0.193
Renal response[a]	8 (27.6)	1 (9.1)	4 (40.0)	0	3 (100)	**0.004**
End-stage kidney disease[a]	7 (24.1)	5 (45.5)	2 (20.0)	0	0	0.140
Lymphoma prior renal impairment						
Yes	21 (61.8)	8 (66.7)	6 (60.0)	4 (66.7)	3 (50.0)	0.960
No	13 (38.2)	4 (33.3)	4 (40.0)	2 (33.3)	3 (50.0)	0.960
Suspected before PKB[a]	8 (61.5)	4 (100)	1 (25.0)	1 (50.0)	2 (66.7)	0.232
Urinary analysis						
Hematuria	14 (41.2)	7 (58.3)	4 (40.0)	3 (50.0)	0	0.155
Proteinuria	22 (64.7)	11 (91.7)	6 (60)	4 (66.7)	1 (16.7)	**0.017**
Glomerular proteinuria[a]	5 (22.7)	2 (18.2)	1 (16.7)	1 (25)	1 (100)	1.000
Mixed proteinuria[a]	12 (54.6)	7 (63.6)	4 (66.6)	1 (25)	0	0.395
Overflow proteinuria[a]	5 (22.7)	2 (18.2)	1 (16.7)	2 (50)	0	0.630
Nephrotic-range proteinuria	4 (11.8)	1 (8.3)	1 (10.0)	1 (16.7)	1 (16.7)	1.000
Leukocyturia	3 (8.8)	1 (8.3)	1 (10.0)	1 (16.7)	0	1.000
Kidney-related clinical features						
HBP	12 (35.3)	4 (33.3)	4 (40.0)	4 (66.7)	0	0.126
Flank pain	1 (2.9)	0	0	1 (16.7)	0	0.353
Oligoanuria	3 (8.8)	2 (16.7)	1 (10.0)	0	0	0.687
Edema	12 (35.3)	6 (50.0)	4 (40.0)	1 (16.7)	1 (16.7)	0.432
Chronic kidney lesions (histology)						
Interstitial	6 (17.6)	4 (33.3)	1 (10.0)	1 (16.7)	0	0.339
Tubular	17 (50.0)	8 (66.7)	6 (60.0)	2 (33.3)	1 (16.7)	0.200
Glomerular	10 (29.4)	6 (50.0)	2 (20.0)	1 (16.7)	1 (16.7)	0.301
Vascular	10 (29.4)	6 (50.0)	3 (30.0)	0	1 (16.7)	0.157
Acute kidney lesions (histology)						
Interstitial	33 (971)	12 (100)	9 (90.0)	6 (100)	6 (100)	0.647
Tubular	9 (26.5)	5 (41.7)	3 (30.0)	1 (16.7)	0	0.294
Glomerular	9 (26.5)	3 (25.0)	3 (30.0)	2 (33.3)	1 (16.7)	1.000
Hematological treatment						
Yes	29 (85.3)	10 (83.3)	7 (70.0)	6 (100)	6 (100)	0.201
Global response (complete response + partial response)[a]	21 (72.4)	5 (50.0)	6 (85.7)	6 (100)	4 (66.7)	0.154

CLL, chronic lymphocytic leukemia; DLBCL, diffuse large B-cell lymphoma; HBP, high blood pressure; NHL, non-Hodgkin lymphoma; PKB, percutaneous kidney biopsy.
[a]Percentages are calculated for the subgroups.
Qualitative data: frequency (%). Significant *P* values are in bold.

Waldenström macroglobulinemia than in the other groups (91.7% vs 16.7%–66.7%) ($P = 0.017$) (Table 2). Radiological abnormalities were detected in 13 patients (38.2%): renal tumors ($n = 6$; 17.6%), perirenal tumors ($n = 3$; 8.8%), urinary tract dilation ($n = 2$; 5.9%), and nephromegaly ($n = 2$; 5.9%). In 5 patients (38.5%), these lesions were bilateral. Lymphadenopathy (61.8%) and extranodal extension (55,9%) were observed in 32 patients. The Ann Arbor classification could be evaluated for 12 patients, and 7 of 12 patients were stage IV.

Kidney Biopsy Histological Analysis

Histological analysis of the kidney biopsies highlighted the presence of diffuse (57.6%) or focal (42.4%) renal interstitial monotypic B-cell infiltration in 33 patients (97.1%), often associated with other renal lesions. The other patient had chronic lymphocytic leukemia and granuloma without cellular infiltration. Multiple epithelioid and gigantocellular non-necrotizing granulomas were found only in patients with chronic lymphocytic leukemia (3 of 10) (Figure 1). Chronic tubular lesions with atrophy/sclerosis were detected in 17 patients (50%), and acute tubular necrosis in 9 patients (26.5%). Severe chronic ischemic lesions were found in 10 patients (29.4%). Glomerular lesions were detected in one-third of patients with chronic ischemic lesions, and acute glomerular lesions in 9 patients (26.5%) (Tables 2, 3, and 4). There was no correlation between clinical and laboratory data (particularly urinalysis abnormalities), renal function, and histological lesions (Table 2).

Renal and Hematological Responses

Among the 29 patients (85.3%; 5 patients did not have any treatment) who received specific

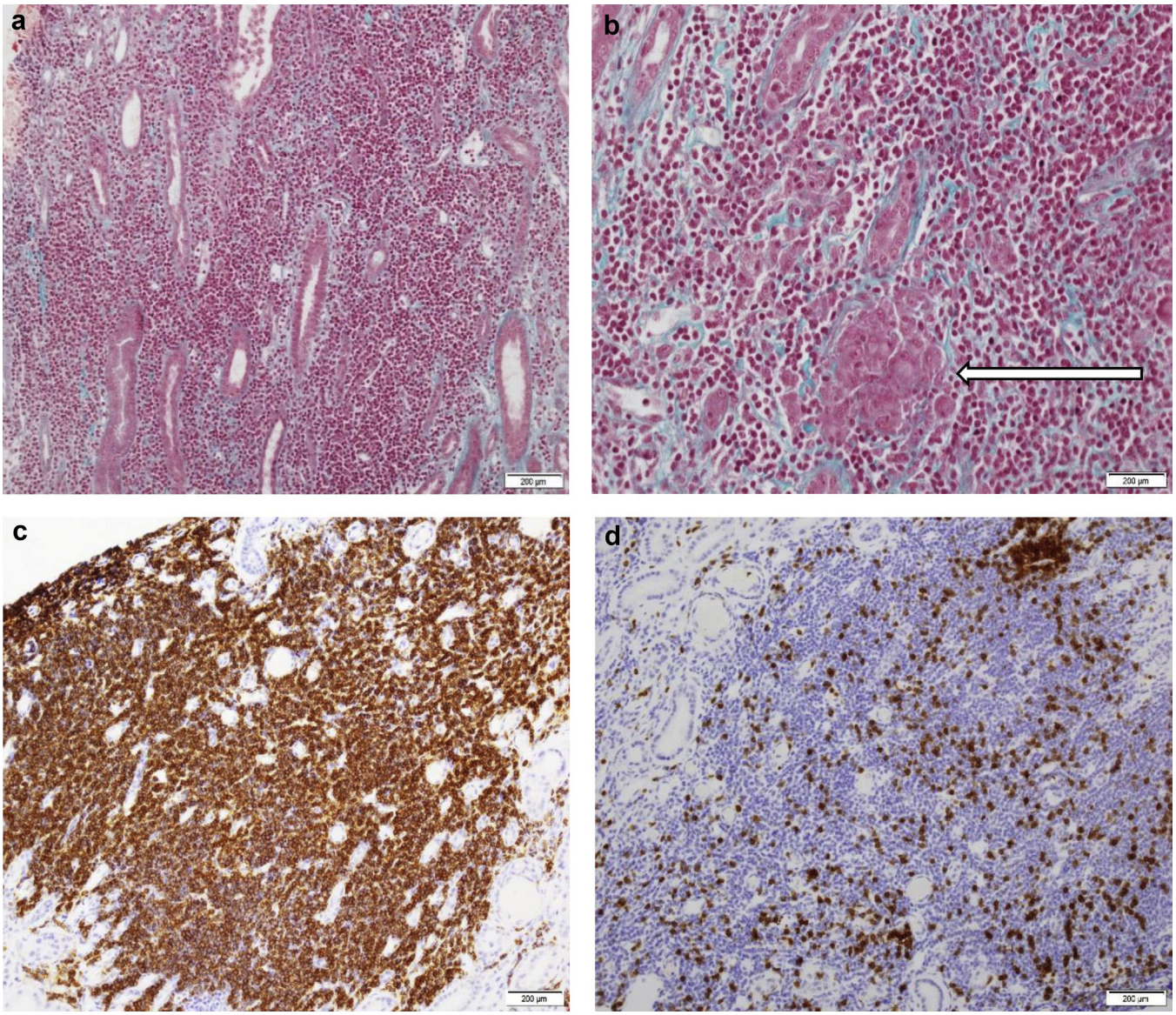

Figure 1. Light microscopy analysis of the kidney biopsy of a patient with CLL and granulomatous reaction. (a,b) Cortical and medullary diffuse lymphoid infiltrate of small B cells, with focal presence of epithelioid and gigantocellular non-necrotizing granulomas (arrow; periodic acid–Schiff). (c,d) Immunohistochemistry analysis highlighted the presence of lymphoid B cells (CD20-positive) (c) and the absence of T cells (CD3-positive) (d).

hematological treatments, 16 showed a CR and 5 a partial remission (Table 5). Most of the treatment regimens included different drugs in combination with rituximab (anti-CD20 monoclonal antibody). Seven patients died during the treatment. Four patients with hematological CR relapsed after a median interval of 20.5 months (1–39), and one of them died just after the relapse. Despite the improvement of the median serum creatinine levels after hematological treatment initiation (219 µmol/L at M1, 153 µmol/L at M6, and 134 µmol/L at M12), the renal response remained poor (n = 8 RR, 27.6%; n = 21 renal nonresponders, 72.4%). At the end of the follow-up, 6 patients had CKD stage 3, 10 patients CKD stage 4, and 7 patients CKD stage 5. Among the 4 patients with nephrotic syndrome, 3 had a CR and 1 a partial remission after hematological treatment.

The only significant predictive factor of renal response was the lymphoma type at diagnosis (P = 0.007), with 100% of RR in patients with high-grade non-Hodgkin lymphoma versus 23.8% for the patients with other lymphoproliferative diseases (P = 0.015). The median survival was 29 months (0.7–119.2) and 12 patients (35.3%) were dead at the end of the follow-up (Figure 2). The causes of death were hematological reasons (n = 5; 41.7%), end-stage renal disease (n = 3, 25%), cardiorespiratory disease (n = 3, 25%), and other malignancy (n = 1, 8.3%). Mortality was higher among renal nonresponders than RR patients (9 vs. 1).

Table 3. Acute renal glomerular lesions according to the lymphoma type

Acute specific glomerular lesions	Waldenström macroglobulinemia, $n = 12$	CLL/lymphocytic lymphoma, $n = 10$	Low-grade NHL, $n = 6$	DLBCL, $n = 6$
Membranoproliferative glomerulonephritis ($n = 3$)	1	1	1	0
Minimal-change disease ($n = 2$)	1	1	0	0
Membranous nephropathy ($n = 1$)	0	1	0	0
Focal segmental glomerulosclerosis ($n = 1$)	0	0	0	1
Light chain deposition disease ($n = 1$)	1	0	0	0
IgA nephropathy ($n = 1$)	0	0	1	0

CLL, chronic lymphocytic leukemia; DLBCL, diffuse large B-cell lymphoma; NHL, non-Hodgkin lymphoma.

DISCUSSION

This study on a large cohort of patients with B-cell lymphoproliferative syndrome and biopsy-proven renal involvement shows that all lymphoproliferative disorders can lead to renal lesions, predominantly infiltration, that may coexist with other glomerular, tubular, and vascular kidney lesions. The most important finding is that the clinical and laboratory presentation did not allow predicting the renal involvement. Consequently, currently, only kidney biopsy can significantly improve the diagnosis, prognosis, and therapeutic decision-making for these patients. Similarly, the hematological response did not consistently predict the renal response, possibly due to the presence also of noninfiltrative renal lesions. Indeed, when B-cell lymphoproliferative syndrome was involved in renal dysfunction, the kidney biopsy almost always revealed renal infiltration that could explain the high frequency of AKI in our cohort (or in these patients if it is a general finding). It also highlighted the frequent concomitant presence of tubular or glomerular lesions, related to the lymphoma or its consequences (e.g., hypercalcemia), or to preexisting chronic injuries (e.g., vascular or glomerular sclerosis). These underlying chronic lesions could limit the renal response to the hematological treatment. Kowalewska

Table 4. Renal pathologic findings in lymphoma-associated disorders

	Whole population ($n = 34$)	Waldenström macroglobulinemia ($n = 12$)	CLL/Lymphocytic lymphoma ($n = 10$)	Low-grade NHL ($n = 6$)	DLBCL ($n = 6$)
Light microscopy					
Sclerotic glomeruli	10 (29.4)	6 (50.0)	2 (20.0)	1 (16.7)	1 (16.7)
Mesangial hypertrophy/hypercellularity	7 (20.6)	3 (25.0)	2 (20.0)	2 (33.3)	0
Endocapillary proliferation	2 (5.9)	1 (8.3)	1 (10.0)	0	0
Glomerular thrombi	2 (5.9)	1 (8.3)	0	1 (16.7)	0
Specific glomerular lesions	9 (26.5)	3 (25.0)	3 (30.0)	2 (33.3)	1 (16.7)
Interstitial fibrosis	20 (58.8)	9 (75.0)	7 (70.0)	3 (50.0)	1 (16.7)
Lymphomatous interstitial infiltration	33 (97.1)	12 (100.0)	9 (90.0)	6 (100.0)	6 (100.0)
Focal[a]	14 (42.4)	4 (33.3)	5 (55.6)	4 (66.7)	1 (16.7)
Diffuse[a]	19 (57.6)	8 (66.7)	4 (44.4)	2 (33.3)	5 (83.3)
Epithelioid and gigantocellular non-necrotizing granuloma	3 (8.8)	0	3 (30.0)	0	0
Tubular atrophy/sclerosis	17 (50.0)	8 (66.7)	6 (60.0)	2 (33.3)	1 (16.7)
Acute tubular necrosis	9 (26.5)	5 (41.7)	3 (30.0)	1 (16.7)	0
Vascular sclerotic lesions	10 (29.4)	6 (50.0)	3 (30.0)	0	1 (16.7)
Composition of deposits by immunofluorescence					
Light chain					
Kappa	12 (35.3)	8 (66.6)	2 (20.0)	2 (33.3)	0
Lambda	9 (26.5)	2 (16.7)	5 (50.0)	2 (33.3)	0
Negative	5 (14.7)	2 (16.7)	2 (20.0)	0 (0.0)	1 (16.7)
Unknown	8 (23.5)	0 (0.0)	1 (10.0)	2 (33.3)	5 (83.3)
Ig					
IgM	9 (26.5)	7 (58.3)	0	1 (16.7)	1 (16.7)
IgG	2 (5.9)	1 (8.3)	1 (10.0)	0	0
IgA	9 (26.5)	4 (33.3)	4 (40.0)	1 (16.7)	0
C3 and/or C1q	17 (50.0)	8 (66.7)	6 (60.0)	2 (33.3)	1 (16.7)
Unknown	9 (26.5)	0	2 (20.0)	2 (33.3)	5 (83.3)
Ultrastructural studies					
Yes	2 (5.9)	0	2 (20.0)	0	0

CLL, chronic lymphocytic leukemia; DLBCL, diffuse large B-cell lymphoma; NHL, non-Hodgkin lymphoma.
[a]Percentages are calculated into the subgroup.
Qualitative data: frequency (%).

Table 5. Comparison between renal responder and renal non-responder patients

Variable	All patients (n = 29)	Renal response		P
		Yes (n = 8)	No (n = 21)	
Sex ratio	29	8	21	0.635
Male/Female	22/7 (75.9%, 24.1%)	7/1 (87.5%/12.5%)	15/6 (71.4%/28.6%)	
Age ≥70 yr	17 (58.6%)	4 (50.0%)	13 (61.9%)	0.683
Performance status > 2	3 (10.3%)	1 (12.5%)	2 (9.5%)	1.000
Renal function impairment				
Acute kidney injury	20 (69.0%)	6 (75.0%)	14 (66.7%)	1.000
Serum creatinine >300 μmol/l	10 (34.5%)	1 (12.5%)	9 (42.9%)	0.201
Inaugural renal impairment	10 (34.5%)	4 (50.0%)	6 (28.6%)	0.390
Preexisting nephropathy	14 (48.3%)	2 (25.0%)	12 (57.1%)	0.215
Morphological abnormalities	9 (31.0%)	3 (37.5%)	6 (28.6%)	0.675
Non-kidney localizations				
1 or 2 sites	4 (13.8%)	0	4 (19.0%)	0.552
>2 sites	17 (58.6%)	7 (87.5%)	10 (47.6%)	0.093
Hematological parameters				
Anemia <10 g/dl	16 (55.2%)	3 (37.5%)	13 (61.9%)	0.406
Bone marrow involvement	22 (84.6%)	4 (66.7%)	18 (90.0%)	0.218
Elevated LDH	9 (34.6)	4 (50.0)	5 (27.8)	0.382
Urinalysis				
Proteinuria >1 g/l	12 (46.2)	2 (40.0)	10 (47.6)	1,000
Nephrotic syndrome	4 (13.8)	2 (25.0)	2 (9.5)	0.300
Hematuria	12 (50.0)	2 (40.0)	10 (52.6)	1.000
Renal histology				
Fibrosis > 50%	6 (20.7)	0	6 (28.6)	0.148
Tubular atrophy	16 (55.2)	3 (37.5)	13 (61.9)	0.406
Vascular lesions	10 (34.5)	2 (25.0)	8 (38.1)	0.675
Ischemic chronic glomerular lesions	10 (34.5)	2 (25.0)	8 (38.1)	0.675
Diagnosis				**0.007**
CLL/lymphocytic lymphoma	10 (34.5)	4 (50.0)	6 (28.6)	
Low-grade NHL	5 (17.2)	0	5 (23.8)	
DLBCL	3 (10.3)	3 (37.5)	0	
Waldenström macroglobulinemia	11 (37.9)	1 (12.5)	10 (47.6)	
Hemopathy prior to PKB	19 (65.5)	4 (50.0)	15 (71.4)	
Hematological response				0.417
Complete response	14 (48.3)	5 (62.5)	9 (42.9)	
Partial response	4 (13.8)	0	4 (19.0)	
Unevaluable	4 (13.8)	1 (12.5)	3 (14.3)	
Progressive disease	6 (20.7)	1 (12.5)	5 (23.8)	
Stability	1 (3.4)	1 (12.5)	0	
End of follow-up				
Death	10 (34.5)	1 (12.5)	9 (42.9)	0.201

CLL, chronic lymphocytic leukemia; DLBCL, diffuse large B-cell lymphoma; LDH, lactate dehydrogenase; NHL, non-Hodgkin lymphoma; PKB, percutaneous kidney biopsy.
Qualitative data: frequency (%).

et al.[8] also found no direct correlation between AKI and the type of detected renal lesions, although proteinuria was correlated with glomerular injury, differently from our study, possibly due to the smaller population. Like in plasma cell dyscrasia, PKB seems essential for the characterization of the renal lesions and fibrosis that might influence the kidney function prognosis. Renal dysfunction can occur at the beginning of the disease (PKB revealed the hematological disease in 38.2% of our patients), or after a long progression of the primary lymphoma (maximum 20 years).[8] Moreover, in the case of hematological neoplasm relapse, PKB remains useful to differentiate active lesions from fibrotic lesions that could explain CKD persistence.

The histological features of our cohort are consistent with the literature data, with a monotypic B-cell infiltrate reaching the interstitium in most patients (97.1%). This infiltrate was mostly diffuse rather than focal, with a focal nodular aspect preferentially found in low-grade lymphomas. Previous studies reported that the renal infiltrate is rather focal in lymphoplasmacytic lymphoma, and diffuse and massive in chronic lymphocytic leukemia.[8,20] In our study, the

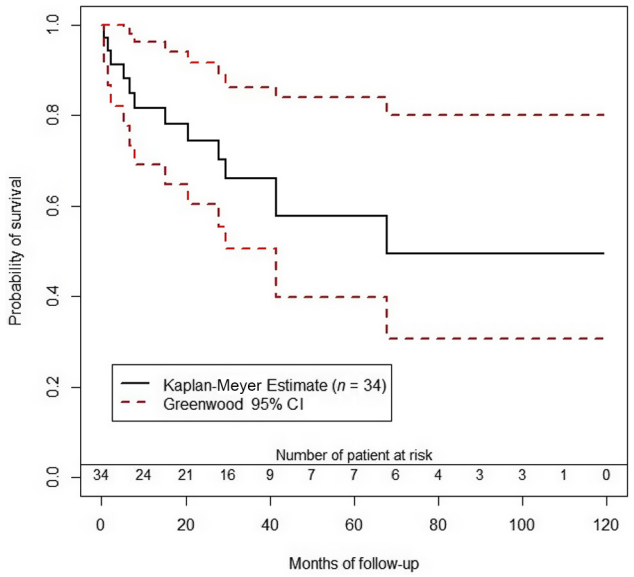

Figure 2. Kaplan-Meyer survival curve. CI, confidence interval.

severity of the initial renal involvement seemed to be correlated with the extent of the lymphomatous infiltrate. This is consistent with other studies, with a serum creatinine level higher than 350 μmol/l in the case of diffuse infiltrate and not exceeding 245 μmol/l in the case of focal infiltrate.[21] The high rate of interstitial infiltrate in our cohort compared with previous studies could be explained by the different inclusion criteria. For instance, Strati *et al.*[9] described patients with chronic lymphocytic leukemia or monoclonal B-cell lymphomatosis who underwent kidney biopsy for renal failure and found a lower rate of infiltrative lesions and some lesions not related to the hematological disorder. On the other hand, Chauvet *et al.*[10] found that interstitial diffuse infiltration was common, even in renal disorders associated with IgM monoclonal gammopathies. Higgins *et al.*[11] included patients with monoclonal IgM protein and availability of a kidney and a bone marrow biopsy, leading to more diverse kidney lesions.

In our cohort, 9 of 34 patients had glomerular lesions (10 of 55 patients in the study by Törnroth *et al.*[5] and 10 of 18 in the study by Kowalewska *et al.*[8]). Different glomerular lesions can be associated with non-Hodgkin lymphoma, among which membranoproliferative glomerulonephritis and membranous nephropathy are the most common,[8,9] whereas minimal-change lesions are uncommon, differently from Hodgkin disease.[22,23] Therefore, the main challenge is to determine the link with the hematological disorder.[24] The definition of paraneoplastic glomerulopathy is based on its chronology, previous pathophysiological suspicion, and concomitant changes of the glomerulopathy and hemopathy on treatment.

Radiological investigations identified kidney anomalies only in one-third of our cohort, although all patients had a histologically proven renal involvement. Contrast-enhanced CT remains the best examination if renal involvement is suspected, but with high risk of renal toxicity.[25,26] Some authors suggested using magnetic resonance imaging, especially in patients with preexisting CKD.[27] The most commonly described morphological abnormalities are multiple parenchymal kidney masses.[28] In our study, only 2 patients (5.9%) presented a typical bilateral kidney enlargement, compared with 21% ($n = 4/19$) in the study by Aymard *et al.*[20] Extrarenal localization was found in most patients in our study (74%), whereas Törnroth *et al.*[5] reported extrarenal involvement in 44% of patients at biopsy time (especially in retroperitoneal lymph nodes). Discrepancies between the radiological and histological findings can be explained by the lower radiology tool sensitivity at the early stages of kidney involvement when the organ morphology is still preserved,[29] and the fact that the radiological picture of renal lymphoma may overlap with that of other diseases, for instance renal cancer or metastases from other tumors.[30] This could also explain the high variability of renal lymphomatous involvement prevalence in the literature, whereas postmortem analysis reported a frequency ranging from 6% to 60%.[2,12,13] The lower sensitivity of radiological tools strengthens the importance of renal biopsy for diagnosis.

In our series, the information provided by PKB led to treatment with corticosteroids or chemotherapy in most patients (85%), as previously reported (95% in the study of Aymard *et al.*,[20] 82% for Törnroth *et al.*[5]). PKB allowed starting treatment earlier (within fewer than 15 days after PKB for 62% of patients). Renal involvement did not seem to influence the chemotherapy choice, especially for aggressive subtypes (all treated according to the standard recommendations), although it is difficult to reach robust conclusions due to the heterogeneity of the cohort and the changes in clinical practices over time. As in the study by Higgins *et al.*,[11] the renal response was not always correlated with the hematological response, probably because of the presence of other renal lesions in addition to infiltration. Among the 72% of patients with an overall hematological response (CR + partial remission), only 1 of 3 showed RR. In the study by Canet *et al.*[31] on 200 patients (53.5% with non-Hodgkin lymphoma), AKI was associated with CR lasting less than 6 months (39.4% vs. 68.3% without AKI, $P < 0.01$) and higher mortality rate (47.4% vs. 30.2%, $P < 0.01$). The independent CR factors were age, high performance status, number of organ dysfunctions, and AKI. Renal

insufficiency was an independent negative prognostic risk factor in the series described by Strati *et al*.[32]

Finally, 23 of 34 patients had CKD at the last follow-up. We tried to evaluate the risk factors associated with CKD, such as age, severity of the initial renal involvement, or abundance of interstitial infiltration. The only prognostic factor of renal response remained the lymphoma subtype, possibly because of the small number of patients in each lymphoma group and therefore the lack of statistical power. Patients with high-grade lymphoma were exclusively in the RR group (3 of 8 patients), probably related to their initial clinical symptomatology that led to a faster diagnosis, and therefore to earlier therapy, and their usually higher chemosensitivity. In the study by Törnroth *et al*.,[5] 43 of the 45 treated patients (95%) were RRs, but their younger median age (45 years compared with 70 years in our study) might suggest fewer chronic renal lesions. The overall survival in our series remained good, and seemed to be correlated with the hematological response, because only 1 of the 16 patients (6%) in the CR group died, compared with 8 of the 11 patients (73%) in the partial response group or with hematological progression.

Our study presents a selection bias because it included only patients with PKB and the "lymphoma" code in the pathology database, possibly explaining the high rate of renal infiltration in our series.[8] Each study has his own bias, according to the inclusion criteria, making comparisons between series difficult.[10,32] For example, Chauvet *et al*.[10] or Higgins *et al*.[11] included patients with monoclonal IgM-secreting B-cell lymphoproliferative disorders, whereas in our study only approximately one-half of the patients had monoclonal gammopathy. It also presents a bias of interpretation because patients with different lymphoma subtypes were included in a single group, although they could have had specific features that could not be identified because of the small size of each subgroup. Moreover, electron microscopy analysis was performed only in w biopsies, although it could have been of great interest for a precise characterization of the deposits. Large descriptive studies are needed to better identify the characteristics of the renal involvement in each of these lymphoma types.

CONCLUSION

Renal involvement in patients with B-cell lymphoma can lead to kidney dysfunction of varying severity through various mechanisms, and remains a major cause of morbidity and mortality. Like for plasma cell dyscrasia, in addition to blood and urine analyses (serum ionogram, creatinine, urine phosphate and calcium, proteinuria with electrophoresis, and urine cytology), kidney biopsy is important to confirm the diagnosis and to visualize the specific or nonspecific acute and/or chronic kidney lesions for rapid treatment initiation. Therefore, it should be proposed at diagnosis of each hemopathy showing radiological or biological signs of renal damage to better preserve the patients' renal function and improve their long-term survival.

DISCLOSURE

All the authors declared no competing interests.

ACKNOWLEDGMENTS

We thank Elisabetta Andermarcher for critical reading and comments on the manuscript.

AUTHOR CONTRIBUTIONS

LC and CV designed the study and wrote the manuscript; all the authors critically revised the manuscript and approved the final version.

REFERENCES

1. Obrador GT, Price B, O'Meara Y, Salant DJ. Acute renal failure due to lymphomatous infiltration of the kidneys. *J Am Soc Nephrol*. 1997;8:1348–1354.
2. Coggins CH. Renal failure in lymphoma. *Kidney Int*. 1980;17:847–855.
3. Scott RB. Leukaemia. *Lancet*. 1957;272:1162–1167.
4. Schwartz JB, Shamsuddin AM. The effects of leukemic infiltrates in various organs in chronic lymphocytic leukemia. *Hum Pathol*. 1981;12:432–440.
5. Törnroth T, Heiro M, Marcussen N, Franssila K. Lymphomas diagnosed by percutaneous kidney biopsy. *Am J Kidney Dis*. 2003;42:960–971.
6. Sellin L, Friedl C, Klein G, et al. Acute renal failure due to a malignant lymphoma infiltration uncovered by renal biopsy. *Nephrol Dial Transplant*. 2004;19:2657–2660.
7. Alkhunaizi AM, Daabil RA, Dawamneh MF. Acute kidney injury secondary to lymphomatous infiltration and the role of kidney biopsy. *Saudi Med J*. 2008;29:1808–1810.
8. Kowalewska J, Nicosia RF, Smith KD, et al. Patterns of glomerular injury in kidneys infiltrated by lymphoplasmacytic neoplasms. *Hum Pathol*. 2011;42:896–903.
9. Strati P, Nasr SH, Leung N, et al. Renal complications in chronic lymphocytic leukemia and monoclonal B-cell lymphocytosis: the Mayo Clinic experience. *Haematologica*. 2015;100:1180–1188.
10. Chauvet S, Bridoux F, Ecotière L, et al. Kidney diseases associated with monoclonal immunoglobulin M–secreting B-cell lymphoproliferative disorders: a case series of 35 patients. *Am J Kidney Dis*. 2015;66:756–767.
11. Higgins L, Nasr SH, Said SM, et al. Kidney involvement of patients with Waldenström macroglobulinemia and other IgM-producing B cell lymphoproliferative disorders. *Clin J Am Soc Nephrol*. 2018;13:1037–1046.

12. Richmond J, Sherman RS, Diamond HD, Craver LF. Renal lesions associated with malignant lymphomas. *Am J Med*. 1962;32:184–207.
13. Humphreys BD, Soiffer RJ, Magee CC. Renal failure associated with cancer and its treatment: an update. *J Am Soc Nephrol*. 2005;16:151–161.
14. Yasunaga Y, Hoshida Y, Hashimoto M, et al. Malignant lymphoma of the kidney. *J Surg Oncol*. 1997;64:207–211.
15. Fernandez-Aceñero MJ, Galindo M, Bengoechea O, et al. Primary malignant lymphoma of the kidney: case report and literature review. *Gen Diagn Pathol*. 1998;143:317–320.
16. Bruch J-F, Duprez-Paumier R, Sizaret D, et al. Étude historique des lymphomes et de leurs classifications. *Rev Francoph Lab*. 2014;2014:59–65.
17. Lister TA, Crowther D, Sutcliffe SB, et al. Report of a committee convened to discuss the evaluation and staging of patients with Hodgkin's disease: Cotswolds meeting. *J Clin Oncol*. 1989;7:1630–1636.
18. Khwaja A. KDIGO clinical practice guidelines for acute kidney injury. *Nephron Clin Pract*. 2012;120:c179–c184.
19. Cheson BD, Pfistner B, Juweid ME, et al. Revised response criteria for malignant lymphoma. *J Clin Oncol*. 2007;25:579–586.
20. Aymard B, Beghoura R, Molina TJ. [Renal infiltrate by a plasmocytoïd chronic B lymphocytic leukaemia and renal failure: a rare occurrence in nephropathology. A case report and review of the literature]. *Nephrol Ther*. 2011;7:479–487 [in French].
21. Da'as N, Polliack A, Cohen Y, et al. Kidney involvement and renal manifestations in non-Hodgkin's lymphoma and lymphocytic leukemia: a retrospective study in 700 patients. *Eur J Haematol*. 2001;67:158–164.
22. Dabbs DJ, Striker LM-M, Mignon F, Striker G. Glomerular lesions in lymphomas and leukemias. *Am J Med*. 1986;80:63–70.
23. Ronco PM. Paraneoplastic glomerulopathies: new insights into an old entity. *Kidney Int*. 1999;56:355–377.
24. Cambier J-F, Ronco P. Onco-nephrology: glomerular diseases with cancer. *Clin J Am Soc Nephrol*. 2012;7:1701–1712.
25. Eisenberg PJ, Papanicolaou N, Lee MJ, Yoder IC. Diagnostic imaging in the evaluation of renal lymphoma. *Leuk Lymphoma*. 1994;16:37–50.
26. Smith PA, Marshall FF, Fishman EK. Spiral computed tomography evaluation of the kidneys: state of the art. *Urology*. 1998;51:3–11.
27. Shi S, Zhou F, Zou W, Wang H. Acute kidney injury and bilateral symmetrical enlargement of the kidneys as first presentation of B-cell lymphoblastic lymphoma. *Am J Kidney Dis*. 2012;60:1044–1048.
28. Urban BA, Fishman EK. Renal lymphoma: CT patterns with emphasis on helical CT. *RadioGraphics*. 2000;20:197–212.
29. Hartman DS, David CJ, Goldman SM, et al. Renal lymphoma: radiologic-pathologic correlation of 21 cases. *Radiology*. 1982;144:759–766.
30. Sheeran SR, Sussman SK. Renal lymphoma: spectrum of CT findings and potential mimics. *AJR Am J Roentgenol*. 1998;171:1067–1072.
31. Canet E, Zafrani L, Lambert J, et al. Acute kidney injury in patients with newly diagnosed high-grade hematological malignancies: impact on remission and survival. *PLoS One*. 2013;8:e55870.
32. Strati P, Chaffee KG, Achenbach SJ, et al. Renal insufficiency is an independent prognostic factor in patients with chronic lymphocytic leukemia. *Haematologica*. 2017;102:e22–e25.