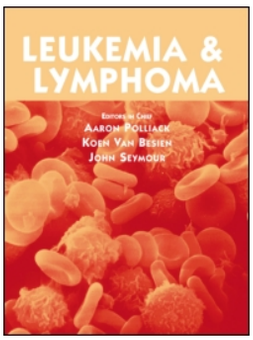

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Leukemia & Lymphoma

ISSN: 1042-8194 (Print) 1029-2403 (Online) Journal homepage: https://www.tandfonline.com/loi/ilal20

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To cite this article: Milena Kohn, Alexandre Karras, Mohamad Zaidan, Charles Bénière, Jean-Baptiste de Fréminville, Kamel Laribi, Marie Claire Perrin, Marion Malphettes, Ronan Le Calloch, Bruno Anglaret, Juliana Martiniuc, Sarah Bailly, Sylvie Chevret, Thierry Molina, Eric Thervet & Catherine Thieblemont (2020): Lymphomas with kidney involvement: the French multicenter retrospective LyKID study, Leukemia & Lymphoma, DOI: 10.1080/10428194.2019.1697811

To link to this article: https://doi.org/10.1080/10428194.2019.1697811

LEUKEMIA & LYMPHOMA
https://doi.org/10.1080/10428194.2019.1697811

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ORIGINAL ARTICLE

Lymphomas with kidney involvement: the French multicenter retrospective LyKID study

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ABSTRACT

The LyKID study is a nationwide survey in France of lymphoma patients with renal involvement based on biopsy and/or imaging, to evaluate its impact on disease outcome and renal function. A total of 87 adult cases of B or T-cell lymphomas were retrospectively analyzed. Interstitial topography was observed in most of the kidney biopsies (54/66; 80%). Kidney failure (glomerular filtration rate <60 mL/min/1.73 m^2) was present in 47% of patients and was associated with non-significantly different outcome. After lymphoma treatment, 44% of patients had persistent chronic kidney failure (CKF); kidney failure at diagnosis was the only parameter associated with CKF in multivariate analysis. DLBCL (diffuse large B-cell lymphomas) represented half of the series, with noticeably CNS (central neurological system) relapse in 17% patients, while fewer than one of two patients had received CNS prophylaxis. To our knowledge, the LyKID study represents the largest published non-autopsy lymphoma series with renal involvement.

ARTICLE HISTORY
Received 25 August 2019
Revised 11 November 2019
Accepted 15 November 2019

KEYWORDS
Lymphoma; chronic kidney failure; prognostic factors; central nervous system relapse; diffuse large B cell lymphoma

Introduction

Autopsy studies carried out in lymphoma patients during the 1960s identified that the kidneys are a possible extra nodal site, with an approximate rate of 35% microscopic renal involvement before imaging staging became routine [1]. Current radiology studies in lymphoma report renal involvement in 3–8% of CT scans in lymphoma patients [2]. Primary renal lymphomas are rare and represent less than 1% of extra nodal non-Hodgkin lymphomas [3]. Therefore, renal involvement mainly occurs in disseminated stage lymphomas.

Clinically, patients with renal lymphoma involvement are generally asymptomatic or may present with back pain and/or hematuria. A range of radiologic presentations have been reported, including a unique mass, multiples masses, or a retroperitoneal mass with contiguous renal involvement, and in some cases hydronephrosis, a perirenal mass, or diffuse nephromegaly is seen [4]. Unlike renal carcinoma, these lesions tend to be hypo vascular. Histologically, two types of lymphoma renal infiltration have been described in the literature: interstitial infiltrate (representing most cases), revealed by non-proteinuric renal failure, and intra-glomerular infiltrate, which is a rare cause of nephrotic syndrome and mostly concerns intravascular large B-cell lymphoma [5]. Differential diagnoses are frequent, and a biopsy is mandatory to confirm the diagnosis of renal lymphoma but is not routinely performed. PET scans can offer some clues by showing more intense uptake in lymphomatous lesions compared to carcinomas [6].

The clinical impact of the renal infiltration on renal function and the patient outcome differs according to histological subtypes. In diffuse large B-cell lymphomas (DLBCL), renal infiltration is rare and is associated with a risk of central nervous system (CNS) relapse as

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Supplemental data for this article can be accessed here.

demonstrated in several large studies [7–11]. A new prognostic score termed the CNS-IPI (central nervous system – international prognostic index), adding kidney and/or adrenal gland involvement to the classical IPI parameters (age, lactate dehydrogenase [LDH], performance status [PS], stage, extra nodal site) was developed to predict CNS relapse in a large cohort of adult patients treated by R-CHOP regimen [12]. In this study, multivariate analysis gave a hazard ratio of 2.8 for renal and/or adrenal gland involvement for predicting CNS relapse ($p = 0.006$). In small B-cell lymphomas, renal infiltration is frequent, reported in up to 50% of patients in an autopsy study [13,14] with many cases reported in the literature. However, the prognostic impact on lymphoma-specific survival and renal function of this infiltration is unknown. In lymphoplasmacytic lymphoma/Waldenström macroglobulinemia (LPL/WM), a recent study shows that lymphoma-caused nephropathy was associated with inferior survival, notably in cases of worsening renal function [15]. In chronic lymphoid leukemia (CLL), renal infiltration is frequent and is not associated with a poorer outcome. In this indolent disease, kidney failure is usually associated with other causes of nephropathy [16–18]. Few cases of renal infiltration by T-cell lymphomas have been published [19,20], and the impact on lymphoma and renal function is unknown.

Causes of kidney failure in the context of lymphoma are multiple, including complications associated with lymphoma (e.g. glomerulopathies, obstruction, thromboses, tumor lysis syndrome, hypercalcemia), and the whole spectrum of acute and chronic interstitial nephropathies. Of note, renal infiltration by lymphomatous cells can lead in some cases to persistent kidney failure, and lymphoma patients are especially at risk of altered renal function from various causes such as age, comorbidities (e.g. hypertension or diabetes), nephrotoxic treatments (chemotherapy, antibiotics), sepsis, metabolic disorders (hypercalcemia, hyperuricemia). Chronic kidney failure (CKF) represents a serious comorbidity for patients (along with an increased risk of cardiovascular events and mortality) and a limitation to therapeutic options for lymphoma treatment - in addition to the burden of chronic dialysis when this is needed.

The main aim of the LyKID study (lymphomas with kidney involvement) was to describe the clinical, biological, radiological and histological characteristics in a large population of adult patients diagnosed with B or T-cell lymphoma and kidney involvement (by biopsy and/or imaging). Secondary objectives were to determine the impact of kidney involvement on lymphoma treatments (chemotherapy posology, CNS prophylaxis), survival, renal outcomes and to identify predictive factors of CKF in these patients.

Materials and methods

Population

We conducted a national retrospective analysis in an adult population of patients managed at LYSA centers (LYmphoma Study Association), diagnosed with B or T-cell lymphoma and kidney involvement (on biopsy and/or imaging by CT or PET-CT scan) at lymphoma diagnosis or relapse. The study was approved by the LYSA scientific committee. Solid organ transplant recipients and patients with other causes of lymphoma-associated nephropathies without lymphomatous infiltrate on the renal biopsy, such as gammopathy-associated glomerulopathy, who represent a distinct nosological entity, were excluded.

Data collection

A questionnaire was sent to all LYSA centers in March 2017. Baseline characteristics of patients (age, sex, history of high blood pressure, diabetes, multiple urinary tract infections), and their disease (histological type according to WHO 2016 classification, and reviewed by expert pathologists within the Lymphopath network) were collected [21]. Ann Arbor stage, ECOG performance status, elevated LDH, IPI were collected from patient medical records and a hospital database (Middlecare, St Louis hospital, Paris). In DLBCL cases, Hans algorithm (germinal center/non-germinal center B-cell like) and major translocations (*MYC/BCL-2/BCL-6* rearrangements) when available were also reported. The type of lymphoma chemotherapy regimen received, the dose adaptation and the CNS prophylaxis (intrathecal chemotherapy and/or intravenous high-dose methotrexate) if administrated were collected, along with the hematological response (reported as complete/partial response or progression). Nephropathy characteristics at the time of diagnosis of renal involvement were collected including blood creatinine, estimated glomerular filtration rate (eGFR) using the MDRD formula, blood albumin, proteinuria, hematuria, leukocyturia, renal imaging, and kidney histology if performed. We also collected whether there was a need for dialysis, and the presence of persisting kidney failure (eGFR <60 mL/min/1.73 m^2) after hematological treatment, defined as CKF. Proteinuria was expressed as the urine protein/creatinine ratio (g/mmol).

Statistical analysis

Time to event parameters were calculated using Kaplan Meier estimates with log-rank tests (overall survival [OS], progression-free survival [PFS], CNS-relapse-free survival). PFS was defined as time to relapse or death, whichever occurred first. CNS-relapse-free survival included only CNS relapses and deaths as events. Comparison of baseline groups were based on Wilcoxon rank sum tests or exact Fisher tests, and a multivariate logistic model was used to summarize predictive factors of renal failure after treatment. All analyses were performed on R 2.14.0 (http://www.R-project.org) statistical software using the R survival package.

Results

Population

A total of 87 patients, from 11 centers in France, Belgium and Switzerland, diagnosed with lymphoma and renal involvement were included in this study (Table 1). Baseline characteristics are presented at time of renal involvement either at first line ($n = 67$, 77%) or at relapse ($n = 20$, 73%) The sex ratio was 2:1 (male to female) and median age was 68 years. In terms of comorbidities associated with renal function impairment, 33% of patients with available data had high blood pressure, 9.6% had diabetes and 5.5% had history of recurrent urinary tract infections. ECOG performance status was 0–1 in 75% of the 72 patients with data. Among patients with available data, LDH was elevated in 56% of cases, Ann Arbor stage was localized (IE) in only five patients (2 DLBCL, 2 LPL/WM, 1 follicular lymphoma, supplementary table S1), and CNS involvement at the time of kidney involvement occurred in two patients.

Hematological disease

The most frequent histological subtype was DLBCL, representing nearly half of the cohort, almost all of whom ($N = 41$) had DLBCL "not otherwise specified" (NOS), while one patient had intravascular large B-cell lymphoma. Among small B-cell lymphomas, there were 13 patients with LPL/WM, 10 patients with follicular lymphoma (FL), 8 patients with small lymphocytic lymphoma/chronic lymphoid leukemia, 5 patients with mantle-cell lymphoma (MCL), 5 with marginal-zone lymphoma, and 4 patients with peripheral T-cell lymphoma.

Table 1. Baseline patient and renal characteristics of the population ($N = 87$).

Characteristic	*N* patients	Median [interquartile] or percentage
Baseline		
Age (median, interquartile), in years	–	68 [60.5;76.5]
Men/women	58/29	67%/33%
Comorbidities		
Arterial hypertension	24/73	33%
Diabetes	7/73	10%
Urinary tract infections	4/73	5.5%
ECOG performance status		
0–1	54/72	75%
2–4	18/72	25%
Elevated LDH	42/75	56%
Ann Arbor stage		
IE	5/76	6.6%
IV	71/76	93%
CNS involvement	2/87	2%
Renal		
eGFR (mL/min/1.73 m^2)	–	60 [32–74]
Kidney involvement		
At initial presentation	67	77%
At lymphoma relapse	20	23%
Kidney failure at diagnosis (eGFR <60 mL/min/1.73 m^2)	37/78	47%
Proteinuria (g/mmol creatininuria)		
>0.03	26/37	70%
0.002–0.03	4/37	19%
<0.002	7/37	11%
Hematuria	15/46	33%
Leukocyturia	11/46	24%
Renal imaging		
Normal	16/78	21%
Unique mass	42/78	54%
Multiple masses	15/78	19%
Perirenal mass	4/78	5.1%
Diffuse nephromegaly	1/78	1.3%
Retroperitoneal mass	0	0%
Renal histology		
Renal histology		
Interstitial infiltrate	54/66	82%
Intra-glomerular infiltrate	1/66	1.5%
Mixed infiltrate	2/66	3.1%
Infiltrate + other cause of lymphoma-associated nephropathy	3/66	4.5%
Infiltrate + carcinoma	6/66	9.1%

CNS: central nervous system; eGFR: estimated Glomerular Filtration Rate according to MDRD formula; LDH: lactate dehydrogenase.

Among the 42 patients with DLBCL, more than 85% had an age adjusted IPI score of 2 or 3 (supplementary Table S2). Germinal center (GC) and non-GC profile according to the Hans algorithm was only available in 23 patients (9 GC subtypes and 14 non-GC). *MYC/BCL2/BCL6* FISH analyses were available in only 9 patients. Two patients had double-hit DLBCL, one with *MYC/BCL2* rearrangement and the other with *MYC/BCL6* rearrangement.

Renal function at diagnosis and imaging

Renal involvement was present at the time of the initial diagnosis of lymphoma in 77% of cases, and at relapse for remaining patients (Table 1). At that time, median eGFR was 60 mL/min/1.73 m^2. Kidney failure,

defined as eGFR <60 mL/min/1.73 m^2, was reported in 47% of patients. Despite rare glomerular modifications on kidney biopsy, proteinuria was frequent, with a urine protein/creatinine ratio above 0.03 g/mmol (equivalent to >0.3 g/day) in more than 70% of patients in which this parameter was measured. In contrast, leukocyturia, which is generally frequent in tubulointerstitial nephropathy, was rare in this patient series, observed in only 24% of patients.

Renal imaging was abnormal in 80% of patients (Table 1). Unique, multiple or perirenal masses were reported in 54%, 19% and 5.1% of cases respectively. Diffuse nephromegaly was observed in one patient. For the 21% of patients with normal imaging, the diagnosis of infiltration was made from the renal biopsy.

Renal histological infiltration

A total of 66 kidney biopsies were available (Table 1). An interstitial infiltrate was present in 82% of cases (see Figure 1(a) for a representative example), with only one case of intra-glomerular cellular infiltration (caused by intravascular B-large cell lymphoma), and two cases of both interstitial and intra-glomerular infiltration. Lymphomatous infiltrate was associated with another cause of lymphoma-associated nephropathy in three patients and/or a carcinoma in six (Figure 1(b) for a representative example).

Treatment response and outcome

Most patients with B-cell lymphomas received combination cytotoxic chemotherapy associated with rituximab (Table 2). The dose of chemotherapy was adapted for 8 of the 42 DLBCL patients during first-line treatment, by reducing either the chemotherapy

Table 2. First-line chemotherapy regimen and dose adaption in DLBCL patients (available data in 29/35 patients).

	N patients (*N* = 29)
Chemotherapy regimen	
R-CHOP	23
R-ACVBP or GA101-ACVBP	4
R-CVP	1
R-DHA	1
Dose adaptation	8
Dose reduction	7
Cycle reduction	1

R: rituximab; GA101: obinutuzumab; CHOP: doxorubicin + cyclophosphamide + vincristine + prednisone; ACVBP: doxorubicin + cyclophosphamide + vindesine + bleomycin + prednisone; CVP: cyclophosphamide + vincristine + prednisone; DHA: dexamethasone + cytarabine.

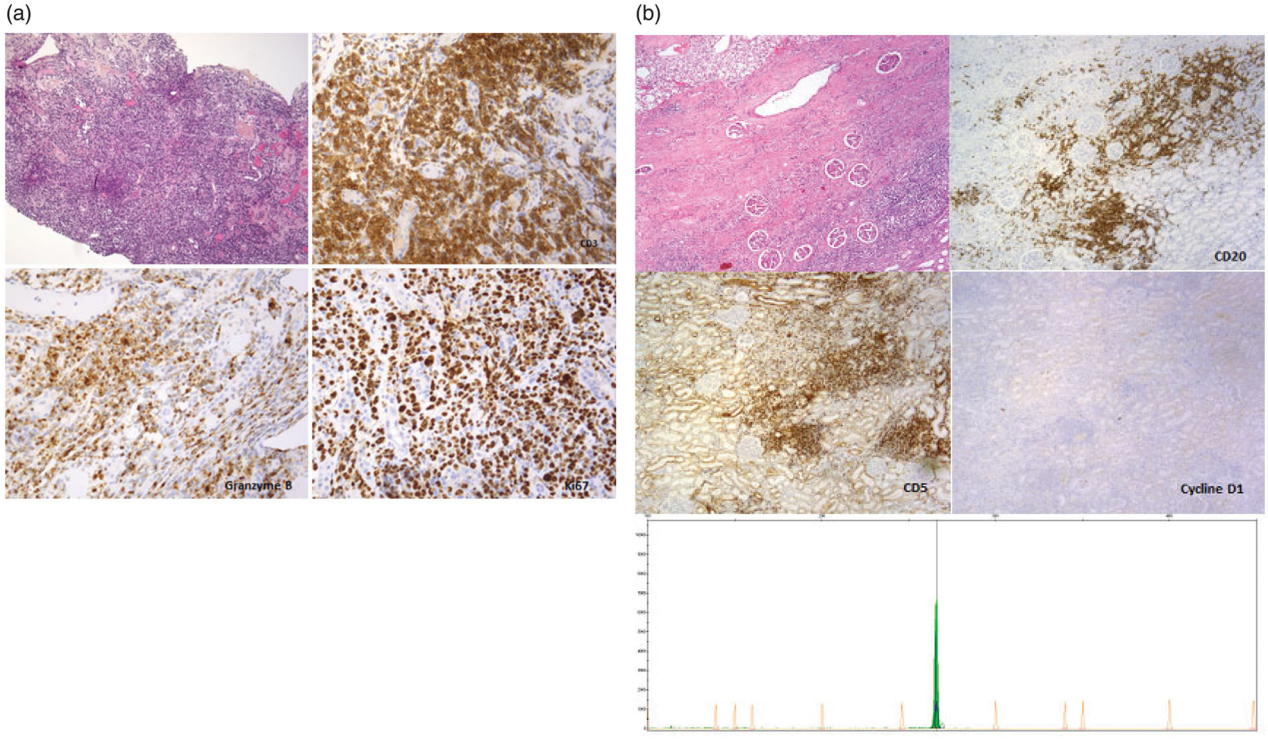

Figure 1. Examples of lymphomatous infiltration in renal biopsies. (a) Diffuse interstitial infiltration by small lymphoid cell proliferation: hematoxylin eosin staining, CD3 staining, granzyme B staining, Ki-67 staining (transformation of large granular lymphocyte leukemia in peripheral T-cell lymphoma NOS). (b) Renal cell carcinoma and small-cell lymphoid infiltrate: Hematoxylin eosin staining, (carcinomatous cells in upper left corner), CD20 staining, CD5 staining, cyclin D1 staining, clonal IGH gene rearrangement clonal (marginal zone lymphoma).

dose (7 patients) or the number of cycles (1 patient). Among the 37 DLBCL patients with available information, 16 received CNS prophylaxis by intrathecal chemotherapy and/or intravenous methotrexate.

Median follow-up duration of the entire cohort was 22 months. Complete response to treatment was reported in 61.6% of patients, partial response in 29.2% and progression in 9.2% of cases. A total of 24 patients experienced relapse, after a median of 11 months. In particular, nine CNS relapses occurred, concerning seven DLBCL patients (representing 16.7% of all DLBCL patients) and two MCL, with a median time to CNS relapse of 11 months. Overall, 25 patients died, with a 5-year OS of 62.9% (95%CI 0.517–0.765) while 5-year PFS was 51.3% (95%CI 0.399–0.661).

Renal function and factors associated with chronic kidney failure

After completion of chemotherapy, 33 out of 75 (44%) patients with available data had altered renal function (defined by an eGFR $<$60 mL/mL/1.73 m^2), including 27 persisting renal failure and 6 patients with worsening renal function; 7/37(19%) patients with initial renal impairment recovered a normal function. Chronic dialysis was necessary in 5 of the 75 (6.7%) patients. When compared to patients without CKF (eGFR $\geq$60 mL/mL/1.73 m^2) after treatment, the population with CKF was older (median age 72 years versus 62 years, $p = 0.002$), was more likely to present with kidney failure ($p < 0.0001$) and without a radiologic renal mass ($p = 0.030$) at diagnosis of renal involvement (Table 3). These patients had a greater tendency towards presenting with high blood pressure ($p = 0.07$). No differences were detected in terms of histological lymphoma subtype, type of renal infiltrate or response to treatment.

In multivariate analysis, only kidney failure at diagnosis remained statistically associated with CKF, with an odds ratio of 34.6 to develop CKF (95%CI 5.15–232.53; supplementary Figure S1**)**. Renal failure at time of lymphoma diagnosis was not associated with a significantly different OS and PFS, with 5-year OS of 56.5% (95%CI, 40.8–78.4%) versus 71.1% (95%CI, 56.4–89.7%) in patients without CKF at diagnosis ($p = 0.18$; Figure 2) and PFS at 5 years with CKF at diagnosis at 45.8% (95%CI, 30.8–68.2%) versus 56.6% (95%CI, 40.4–79.6%) in patients without ($p = 0.41$).

Table 3. Univariate analysis of factors associated with renal outcome (clinical, biological, histology, lymphoma).

Characteristic	eGF*R* $\geq$60mL/min after treatment *N* = 42/75	eGF*R* $<$ 60mL/min after treatment *N* = 33/75	*p* Value
Age (years) (mean ± SD)	62.0 ± 1.8	72.2 ± 1.7	0.0002*
Male sex	29/42 (69.1%)	21/33 (63.6%)	0.63
High blood pressure	9/40 (22.5%)	14/31 (45.2%)	0.07
Diabetes	5/40 (10.0%)	2/31 (6.5%)	0.70
Urinary tract infections	1/40 (2.5%)	3/31 (9.7%)	0.31
Kidney failure at diagnosis	7/41 (17.1%)	27/33 (81.8%)	<0.0001*
Proteinuria	9/15 (60.0%)	16/20 (80.0%)	0.27
Micro-albuminuria	4/15 (26.7%)	3/20 (15.0%)	0.43
Leukocyturia	4/19 (21.01%)	6/25 (24.00%)	>0.99
Hematuria	8/20 (40.0%)	7/26 (26.9%)	0.53
Normal renal imaging	5/42 (11.9%)	10/31 (32.3%)	0.03
Unique mass	23/42 (54.8%)	15/31 (48.4%)	0.59
Multiple masses	10/42 (23.8%)	5/31 (16.1%)	0.42
Perirenal mass	4/42 (9.5%)	0/31 (0%)	0.08
Nephromegaly	0/42 (0%)	1/31 (3.2%)	0.24
Interstitial renal infiltration	24/27 (88.9%)	23/27 (85.2%)	>0.99
Glomerular renal infiltration	0/27 (0%)	1/27 (3.7%)	>0.99
Mixed renal infiltration	0/27 (0%)	2/27 (7.4%)	0.49
+carcinoma	2/27 (7.4%)	0/27 (0%)	0.49
+other cause	0/27 (0%)	1/27 (3.7%)	>0.99
DLBCL	20/42 (47.6%)	17/33 (51.5%)	0.82
LPL/WM	4/42 (9.5%)	6/33 (18.2%)	0.27
Follicular lymphoma	7/42 (16.7%)	3/33 (9.1%)	0.50
Mantle-cell lymphoma	4/42 (9.5%)	1/33 (3.0%)	0.38
Marginal-zone lymphoma	3/42 (7.1%)	1/33 (3.0%)	0.63
Chronic lymphoid leukemia	3/42 (7.1%)	2/33 (6.1%)	>0.99
T cell lymphoma	3/42 (7.1%)	1/33 (3.0%)	0.63
Elevated LDH	21/40 (52.5%)	19/30 (63.3%)	0.47
Renal inv at initial presentation	33/42 (78.6%)	26/33 (78.8%)	>0.99
Renal inv at relapse	9/42 (21.4°/%)	7/33 (21.2%)	>0.99
Complete response	24/39 (61.5%)	16/26 (61.5%)	>0.99
Partial response	13/39 (33.3%)	6/26 (23.1%)	0.42
Progression	2/39 (5.1%)	4/26 (15.4%)	0.21

DLBCL: diffuse large B cell lymphoma; inv: involvement; LPL/WM: lymphoplasmacytic lymphoma/Waldenström macroglobulinemia.
*Statistically significant.

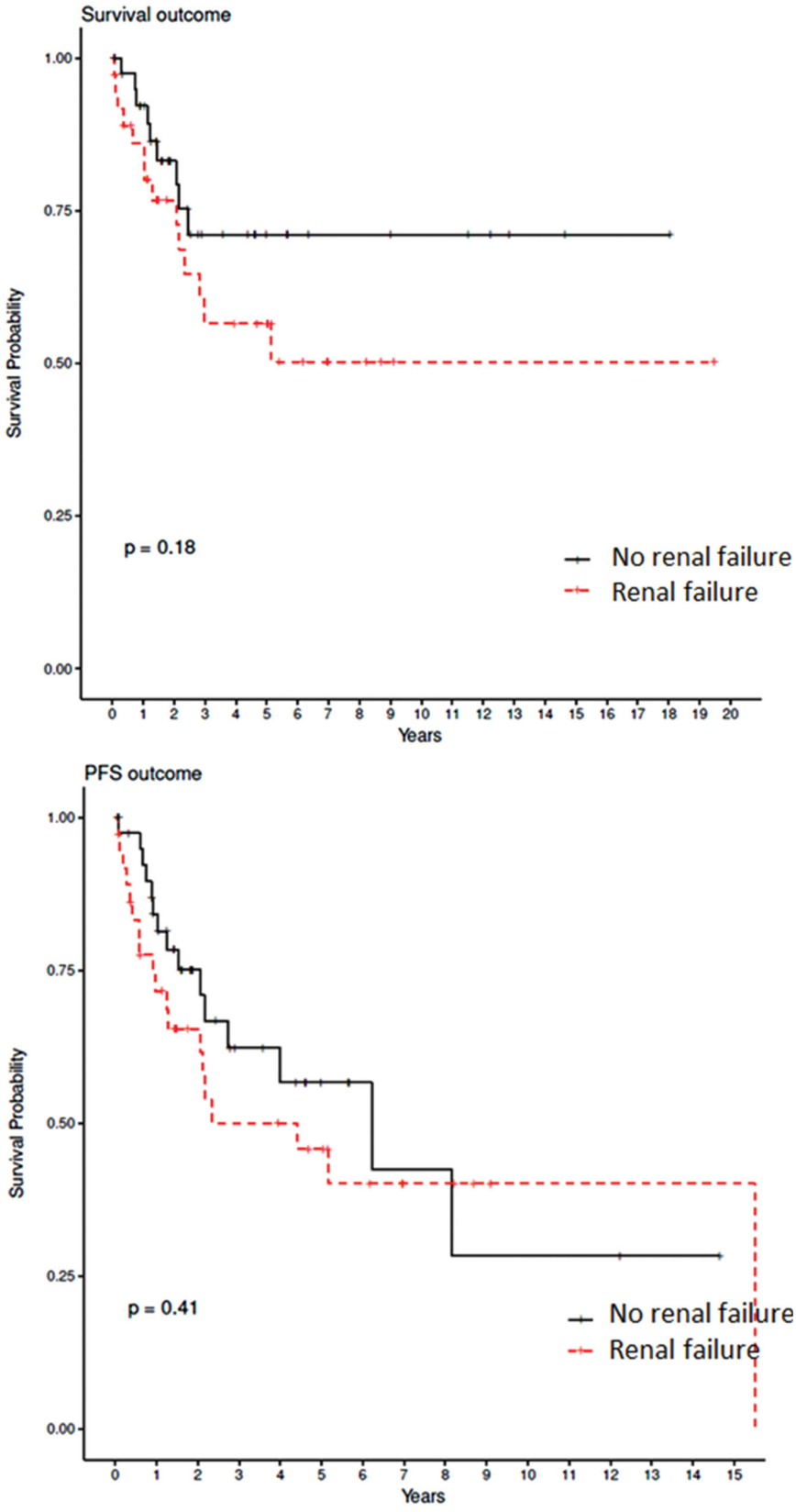

Figure 2. Kaplan-Meier estimates of OS (upper panel) and PFS (lower panel) according to the presence of renal failure at lymphoma diagnosis.

Discussion

To our knowledge, the LyKID study represents the largest published non-autopsy lymphoma series with renal involvement [7,11,15,18,22,23] (supplementary Table S3). Only five of the 87 patients in the cohort were diagnosed with primary lymphomas (two DLBCL, two lymphoplasmacytic lymphoma and one follicular lymphoma), in line with the fact that most lymphomas with kidney involvement present at a disseminated stage. Radiological presentations vary, with numerous differential diagnoses, making kidney biopsy mandatory in the context of a renal mass or in case of renal failure of undetermined origin.

Most of the renal biopsies showed an interstitial infiltration; only one case of pure intra-glomerular infiltrate was identified in the cohort, with a diagnosis of intravascular large B-cell lymphoma (as already reported in the literature). Carcinoma associated with lymphomatous infiltrate was found in six patients, supporting the hypothesis of the presence of common genetic and/or environmental factors [24].

Half of the patients presented with renal failure at diagnosis and renal function remained impaired in 44% despite specific therapy for their lymphoma. The population of patients with altered renal function after chemotherapy were older, and high blood pressure was more frequent. At the time of diagnosis, they presented with renal failure and normal renal imaging. Only the presence of initial renal failure was associated with persistence of CKF in the multivariate logistic model. There was no significant difference in overall and progression-free survival between patients with and without renal failure at diagnosis.

DLBCL represented half of the series, with noticeably CNS relapse in seven patients (17%), while fewer than one of two patients had received CNS prophylaxis (irrespective of the nature of prophylaxis). These patients exhibited equivalent survival as in large published series of patients with a higher risk of CNS relapse [25,26]. We also observed two CNS relapses among our five MCL patients. In the literature, the CNS relapse rate in MCL is 4.1–7.8%, with identified risk factors being blastoid subtype, elevated MCL IPI (MIPI) score, elevated LDH and high Ki67 [27–29]. Due to the low numbers of cases in the LyKID study, we cannot conclude over higher CNS relapse risk in cases of renal involvement, but this should be further verified in largest cohorts.

Limitations of the LyKID study include a selection bias because the renal involvement was collected heterogeneously by hematologists, nephrologists, pathologists and analysis of hospital databases, including newly diagnosed and relapsed lymphomas. Secondly, the high rate of kidney biopsies in this series does not reflect usual clinical practice. In most hematology centers, kidney biopsies are rarely performed especially when a PET scan shows a more accessible site for biopsy (peripheral adenopathy) and/or when initial renal dysfunction and/or kidney radiological abnormalities improve with treatment. Finally, several patients were lost to follow-up, and there was a high level of missing data for urine tests, rendering detailed analysis impossible.

Considering these results, our recommendation for treatment management of a patient with lymphoma renal involvement (preferably diagnosed on a kidney biopsy) is to perform blood and urine evaluations including serum creatinine measurement (and an estimation of GFR by the MDRD or CKD-EPI formula), spot urine protein to creatinine ratio (normal if <0.002 g/mmol) and urine sediment to check for hematuria and leukocyturia. If tests prove abnormal, we recommend additional monitoring at middle and end of treatment. If abnormalities persist (eGFR >60 mL/min/1.73 m^2, proteinuria/creatininuria >0.03 g/mmol, hematuria,

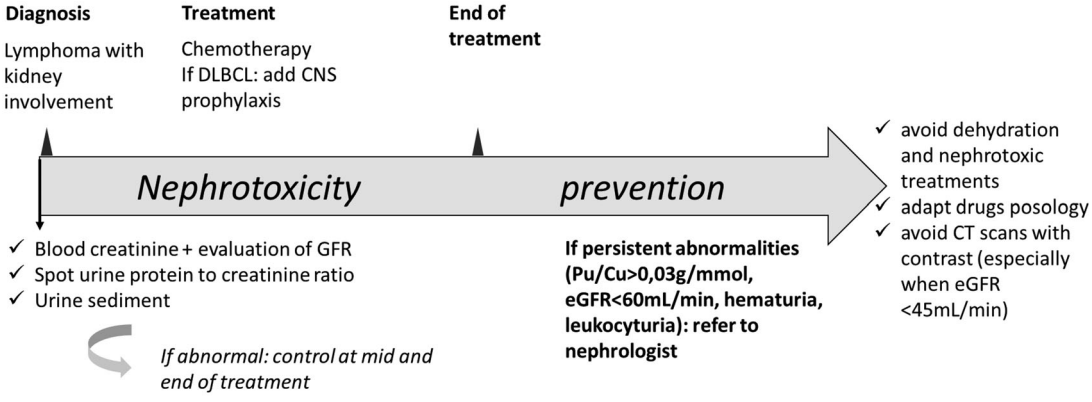

Figure 3. Management of patients with lymphoma renal involvement. eGFR: glomerular filtration rate; CNS: central nervous system; DLBCL: diffuse large B-cell lymphoma, Pu/Cu: spot urine to creatinine ratio.

leukocyturia), the patient should be referred to a nephrologist for nephroprotective measures (hypertension/diabetes management, angiotensin converting enzyme inhibitor prescription). Nephrotoxicity must be prevented by avoiding situations of dehydration and nephrotoxic treatments, adapting drug posology when necessary, and avoiding if possible, CT scans with iodine contrast media, especially when eGFR is <45 mL/min/1.73 m^2. For DLBCL patients, we strongly recommend administering CNS prophylaxis because of the high rate of relapses (Figure 3).

In conclusion, the LyKID study highlights the diversity of the clinical presentations of renal involvement in lymphoma patients. It has significant impact on lymphoma outcome and is associated with frequent persistent alteration of renal function, even after successful treatment of the hematological malignancy. Early referral to nephrologists should be discussed in patients with significant renal dysfunction to optimize long-term nephroprotection.

Acknowledgments

The authors thank all the LYSA centers who were involved in the LyKID study, particularly the clinical research assistants who helped to collect the data and the scientific committee for their advice.

Disclosure statement

No potential conflict of interest was reported by the authors.

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References

[1] Richmond J, Sherman RS, Diamond HD, et al. Renal lesions associated with malignant lymphomas. Am J Med. 1962;32(2):184–207.
[2] Sandrasegaran K, Menias CO, Verma S, et al. Imaging features of haematological malignancies of kidneys. Clin Radiol. 2016;71(3):195–202.
[3] Okuno SH, Hoyer JD, Ristow K, et al. Primary renal non-Hodgkin's lymphoma. An unusual extranodal site. Cancer. 1995;75(9):2258–2261.
[4] Urban BA, Fishman EK. Renal lymphoma: CT patterns with emphasis on helical CT. Radiogr Rev Publ Radiol Soc N Am Inc. 2000;20(1):197–212.
[5] Törnroth T, Heiro M, Marcussen N, et al. Lymphomas diagnosed by percutaneous kidney biopsy. Am J Kidney Dis off J Natl Kidney Found. 2003;42(5):960–971.
[6] Nicolau C, Sala E, Kumar A, et al. Renal masses detected on FDG PET/CT in patients with lymphoma: imaging features differentiating primary renal cell carcinomas from renal lymphomatous involvement. AJR Am J Roentgenol. 2017;208(4):849–853.
[7] Morel P, Dupriez B, Herbrecht R, et al. Aggressive lymphomas with renal involvement: a study of 48 patients treated with the LNH-84 and LNH-87 regimens. Groupe d'Etude des Lymphomes de l'Adulte. Br J Cancer. 1994;70(1):154–159.
[8] van Besien K, Ha CS, Murphy S, et al. Risk factors, treatment, and outcome of central nervous system recurrence in adults with intermediate-grade and immunoblastic lymphoma. Blood. 1998;91(4):1178–1184.
[9] Haioun C, Besson C, Lepage E, et al. Incidence and risk factors of central nervous system relapse in histologically aggressive non-Hodgkin's lymphoma uniformly treated and receiving intrathecal central nervous system prophylaxis: a GELA study on 974 patients. Groupe d'Etudes des Lymphomes de l'Adulte. Ann Oncol off J Eur Soc Med Oncol ESMO. 2000;11(6):685–690.
[10] Boehme V, Zeynalova S, Kloess M, et al. Incidence and risk factors of central nervous system recurrence in aggressive lymphoma–a survey of 1693 patients treated in protocols of the German High-Grade Non-Hodgkin's Lymphoma Study Group (DSHNHL). Ann Oncol off J Eur Soc Med Oncol ESMO. 2006;18(1):149–157.
[11] Villa D, Connors JM, Sehn LH, et al. Diffuse large B-cell lymphoma with involvement of the kidney: outcome and risk of central nervous system relapse. Haematologica. 2011; 96(7):1002–1007.
[12] Schmitz N, Zeynalova S, Nickelsen M, et al. CNS international prognostic index: a risk model for CNS relapse in patients with diffuse large B-cell lymphoma treated with R-CHOP. JCO. 2016;34(26):3150–3156.
[13] Xiao JC, Walz-Mattmüller R, Ruck P, et al. Renal involvement in myeloproliferative and lymphoproliferative disorders. A study of autopsy cases. Gen Diagn Pathol. 1997;142(3-4):147–153.
[14] Garcia M, Konoplev S, Morosan C, et al. MALT lymphoma involving the kidney: a report of 10 cases and review of the literature. Am J Clin Pathol. 2007;128(3):464–473.
[15] Vos JM, Gustine J, Rennke HG, et al. Renal disease related to Waldenström macroglobulinaemia: incidence, pathology and clinical outcomes. Br J Haematol. 2016;175(4):623–630.
[16] Schwartz JB, Shamsuddin AM. The effects of leukemic infiltrates in various organs in chronic lymphocytic leukemia. Hum Pathol. 1981;12(5):432–440.
[17] Barcos M, Lane W, Gomez GA, et al. An autopsy study of 1206 acute and chronic leukemias (1958 to 1982). Cancer. 1987;60(4):827–837.
[18] 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(9):1180–1188.
[19] Ong DM, Cummins KD, Pham A, et al. PAX5-expressing ALK-negative anaplastic large cell lymphoma with extensive extranodal and nodal involvement. BMJ Case Rep. 2015;2015:bcr2015211159.

[20] Burg G. Systemic involvement in mycosis fungoides. Clin Dermatol. 2015;33(5):563–571.
[21] Laurent C, Baron M, Amara N, et al. Impact of expert pathologic review of lymphoma diagnosis: study of patients from the French lymphopath network. JCO. 2017;35(18):2008–2017.
[22] Li S-J, Chen H-P, Chen Y-H, et al. Renal involvement in non-Hodgkin lymphoma: proven by renal biopsy. *PloS One*. 2014;9(4):e95190.
[23] Poitou-Verkinder A-L, Francois A, Drieux F, et al. The spectrum of kidney pathology in B-cell chronic lymphocytic leukemia/small lymphocytic lymphoma: a 25-year multicenter experience. *PloS One*. 2015;10(3):e0119156.
[24] Kunthur A, Wiernik PH, Dutcher JP. Renal parenchymal tumors and lymphoma in the same patient: case series and review of the literature. Am J Hematol. 2006;81(4):271–280.
[25] Coiffier B, Thieblemont C, Van Den Neste E, et al. Long-term outcome of patients in the LNH-98.5 trial, the first randomized study comparing rituximab-CHOP to standard CHOP chemotherapy in DLBCL patients: a study by the Groupe d'Etudes des Lymphomes de l'Adulte. Blood. 2010;116(12):2040–2045.
[26] Vitolo U, Trněný M, Belada D, et al. Obinutuzumab or rituximab plus cyclophosphamide, doxorubicin, vincristine, and prednisone in previously untreated diffuse large B-cell lymphoma. JCO. 2017;35(31):3529–3537.
[27] Cheah CY, George A, Giné E, et al. Central nervous system involvement in mantle cell lymphoma: clinical features, prognostic factors and outcomes from the European Mantle Cell Lymphoma Network. Ann Oncol off J Eur Soc Med Oncol. 2013;24(8):2119–2123.
[28] Conconi A, Franceschetti S, Lobetti-Bodoni C, et al. Risk factors of central nervous system relapse in mantle cell lymphoma. Leuk Lymphoma. 2013;54(9):1908–1914.
[29] Chihara D, Asano N, Ohmachi K, et al. Ki-67 is a strong predictor of central nervous system relapse in patients with mantle cell lymphoma (MCL). Ann Oncol off J Eur Soc Med Oncol. 2015;26(5):966–973.