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Clinicopathological spectrum of renal parenchymal involvement in B-cell lymphoproliferative disorders

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Abstract

The clinicopathological characteristics of kidney infiltration in B-cell lymphoproliferative disorders remain poorly described. We retrospectively studied 52 adults with biopsy-proven malignant B-cell kidney infiltration, including Waldenström's macroglobulinemia (n=21), chronic lymphocytic leukemia (n=11), diffuse large B-cell lymphoma (DLBCL) (n=8), other lymphoma (n=11), and multiple myeloma (n=1). Kidney disease varied according to the underlying lymphoproliferative disorder. In DLBCL, malignant kidney infiltration was prominent, resulting in acute kidney injury (AKI, 75%) and kidney enlargement (88%). In the other types, associated immunoglobulin-related nephropathy (most commonly AL amyloidosis) was more common (45%), and chronic kidney disease with proteinuria was the primary presentation. All patients received chemotherapy. Over a median follow-up of 31 months, 20 patients died and 21 reached end-stage kidney disease. Renal response, achieved in 25 patients (48%), was associated with higher overall survival (97 vs. 37 months in non-renal responders). In univariate analysis, percentage of sclerotic glomeruli, kidney enlargement, and complete hematological response at 6 months were predictive of renal response. In multivariate analysis, concomitant immunoglobulin-related nephropathy was the sole independent predictor of poor renal outcome. In conclusion, clinical presentation of renal lymphomatous infiltration depends on the nature of the underlying lymphoproliferative disorder. In DLBCL, massive renal infiltration manifests with enlarged kidneys and AKI, and the diagnosis primarily relies on lymph node biopsy. In other B-cell lymphoproliferative disorders, the clinicopathological spectrum is more heterogeneous, with a high frequency of immunoglobulin-related nephropathy that may affect renal outcome; thus kidney biopsy is required for early diagnosis and prognostic assessment.

Keywords: Acute kidney injury, B-cell lymphoma, kidney biopsy, monoclonal gammopathy

Translational Statement:

Our study highlights the heterogeneous presentation and prognosis of patients with B-cell lymphoproliferative disorders and renal parenchymal infiltration. Because concurrent kidney disease related to secreted toxic monoclonal immunoglobulins is common and negatively affects renal outcome, future studies are needed to optimize therapeutic strategy and rapidly reduce the level of the circulating paraprotein. Thus, collaborative work between nephrologists and hematologists seems crucial to improve patient care.

Introduction

Renal disease is a frequent complication of B-cell lymphoproliferative disorders, including multiple myeloma (MM), Waldenström's macroglobulinemia (WM), and other non-Hodgkin lymphomas (NHL).[1-5] Il may result from two main pathophysiological mechanisms that may coexist in the same patient, i.e. malignant infiltration of the renal tissue by clonal B-cells, and toxicity of monoclonal immunoglobulin (Ig) secreted by the clone. Whereas, the first is related to malignant tumor burden, the second is driven by structural peculiarities of the monoclonal Ig. [6-8]

Most renal lesions related to pathogenic monoclonal Ig occur in patients with an indolent B-cell lymphoid disorder or monoclonal gammopathy of undetermined significance (MGUS). These disorders are triggered by physicochemical characteristics of the secreted monoclonal Ig, rather than tumor mass. The term monoclonal gammopathy of renal significance (MGRS) was recently introduced to distinguish these conditions from the benign hematological disorder MGUS that is not associated with any organ damage.[6,7] The spectrum of renal lesions in MGRS covers tubular, i.e. light-chain proximal tubulopathy (LCPT), and glomerular disorders. The latter are classified according to their ultrastructural characteristics, with either organized (AL amyloidosis, cryoglobulinemic glomerulonephritis, immunotactoid glomerulopathy), amorphous Ig deposits (monoclonal Ig deposition disease and proliferative glomerulonephritis with monoclonal immunoglobulin deposits), or deposits of C3 only (C3 glomerulopathy).[8] The usual presentation is chronic kidney disease (CKD), variably associated with symptoms of proximal tubule dysfunction in LCPT, and proteinuria sometimes in nephrotic range in glomerular disorders. Less commonly, patients may present with rapidly progressive glomerulonephritis, particularly in type 1 and type 2 cryoglobulinemic glomerulonephritis and C3 glomerulopathy.

Renal disease in B-cell lymphoproliferative disorders may also result from direct or indirect consequences of uncontrolled clonal expansion in patients with symptomatic hematological disease. Most patients present with acute kidney injury (AKI). AKI can result from treatment-related complications such as infection and toxicity of chemotherapy.[9] Causes of AKI directly related to high tumor mass include hypercalcemia, tumor lysis syndrome, urinary tract obstruction by lymph nodes and cast nephropathy induced by monoclonal light chain (LC) precipitation with uromodulin in distal tubule lumens during symptomatic MM secreting large amounts of free LC.[10] Intra-capillary thrombi of monoclonal IgM were commonly reported in WM with hyperviscosity syndrome, but there incidence has decreased with modern management.[5,11,12] Another classical mechanism of renal disease in symptomatic B-cell lymphoproliferative disorders is malignant infiltration of the renal parenchyma.

Although the kidney itself is devoid of significant lymphoid tissue, data from autopsy studies indicate that this complication is frequent in patients with advanced lymphomas. In a study of 120 patients with various hematological malignancies, post-mortem pathologic studies revealed tumor infiltration of the kidneys in 34% of cases, ranging from 10% to 50% in patients with high-grade and low-grade NHL, respectively.[13] In chronic lymphocytic leukemia (CLL), the prevalence of renal parenchymal infiltration ranged from 63% to 93% in autopsy series.[13-15] To date, AKI and bilateral kidney enlargement are considered as the characteristic manifestations of lymphomatous renal infiltration.[16,17] The full spectrum of renal infiltration in B-cell lymphoproliferative disorders remains poorly described and few data are available on renal and patient outcomes. Morever, little is known about the influence of the type of B-cell clonal proliferation on renal presentation and outcomes. We herein report the results of a large multicenter retrospective study of patients with biopsy-proven tumor B-cell infiltration of renal parenchyma with particular focus on renal presentation and prognosis according to each type of lymphoproliferative disease.

Results

Demographics and baseline patients' characteristics

Baseline clinical and biological data of the whole cohort (including 31 males and 21 females, median age 65 years [range, 17-90]) are summarized in Table 1. Twenty patients (38%) had previously known CKD, stage II (n=8), stage III (n=9) , or stage IV (n=3). Eleven patients (21%) had a past history of hypertension and/or diabetes mellitus.

Renal manifestations

At the time of kidney biopsy, 29 patients (56%) presented with AKI, 18 of whom with KDIGO score 3. Six patients (12%) required hemodialysis upon admission. Thirty-five patients (67%) had >1g/day proteinuria, with nephrotic syndrome in 18 cases (35%), and microhematuria in 30 cases (58%). Two patients displayed proximal tubule dysfunction with normoglycemic glycosuria, generalized aminoaciduria, and increased fractional excretion of phosphate and uric acid. Imaging studies revealed morphological abnormalities in 11 patients (21%), with unilateral (n=1) or bilateral (n=10) kidney enlargement (Table 1). Of these, 7 had DLBCL. Retroperitoneal invasion was diagnosed in 3 patients. None showed retroperitoneal fibrosis or urinary tract obstruction. In 37 patients (71%), including 3 patients with primary renal lymphoma, renal symptoms were the first manifestation of the underlying hematological malignancy.

Hematological and immunological studies

The most frequent hematological diagnosis was WM (n=21, 40%), followed by CLL/small lymphocytic lymphoma (SLL) (n=11, 21%), diffuse large B-cell lymphoma (DLBCL) (n=8, 15%), and various other B-cell NHL (follicular lymphoma, n=5; marginal zone lymphoma, n=3; mantle-cell lymphoma, n=3). Only one patient presented with symptomatic

IgAλ MM without detectable circulating plasma cells. One patient presented with intra-vascular large B-cell lymphoma and 3 patients had primary renal lymphoma, including follicular lymphoma in 2, and SLL in 1 patient. Most patients had high tumour burden with disseminated disease and with high international prognostic scores (Table 1). In 15 patients (29%), the hematological diagnosis preceded renal manifestations, within a median time of 43 months.

A serum monoclonal Ig was detected in 38 cases (73%). The isotype was IgM (n=26, 68%), IgG (n=9, 24%) and IgA (n=3, 8%). The LC isotype was κ in 68% of cases. Bence-Jones proteinuria was detected in 28 patients (54%) (Table 1). Type 1 IgM cryoglobulinemia was identified in two patients (WM, n=1; follicular lymphoma, n=1).

Pathological findings

The most common lesions were tubulointerstitial malignant infiltration, diffuse (n=40) or focal (n=11), that consisted of lymphoid (n=29), lymphoplasmacytic (n=21) or plasma (n=1) cells (Figure 1). One patient had lymphoid infiltration restricted to glomerular and peritubular capillary lumens consistent with intravascular B-cell lymphoma (Figure 2). Five patients, including one with symptoms of proximal tubular dysfunction, showed severe tubulitis consistent with malignant cells within the tubular epithelium and 11 patients displayed glomerular intracapillary infiltration by lymphomatous cells (Table 2). Lymphomatous involvement of peri-renal adipose tissue and renal capsule was observed in 11 (21%) and 26 patients (50%), respectively. Immunophenotypic analysis of renal infiltrate was available in 50 patients. Forty-nine patients showed positive staining for B-cell markers, consistent with bone marrow immunochemistry results in all cases. In the sole patient with MM, diffuse interstitial infiltrate by CD138 positive plasma cells coexisted with glomerular, vascular and peritubular λ amyloid AL deposits (Figure 3).

Other renal lesions related to the B-cell neoplasm were found in 20 patients (38%) (Table 2). One patient with marginal zone lymphoma had paraneoplastic membranous

nephropathy with polyclonal IgG deposits, whereas 19 patients had lesions related to the monoclonal Ig secreted by the B-cell clone (Table 2). Of these, 17 had a detectable serum and/or urine monoclonal component by immunofixation. AL-amyloidosis was the most common diagnosis, reported in 6 cases (WM, n=5; MM, n=1). Three patients had numerous kappa (n=2) or lambda (n=1) restrictive casts within distal tubule lumens, characteristic of associated cast nephropathy (WM, n=2, CLL, n=1). One patient with WM had kappa LC-associated Fanconi syndrome with characteristic intracytoplasmic crystalline inclusions within proximal tubular by EM. Monoclonal Ig deposition disease with linear kappa deposits along glomerular and tubular basement membranes was found in two patients (follicular lymphoma, n=1; WM, n=1). Renal thrombotic microangiopathy, without evidence of hemolysis and schistocytosis, was diagnosed in one patient with WM. Six patients had membranoproliferative glomerulonephritis (MPGN) with monoclonal Ig deposits. Of these, type 1 IgMλ cryoglobulinemic glomerulonephritis was diagnosed in 2 cases (WM, n=1; CLL, n=1) and type 2 IgMλ anti-IgG cryoglobulinemic glomerulonephritis in one patient with mantle cell lymphoma; two patients with CLL had glomerulonephritis with organized microtubular monoclonal IgG1λ deposits (immunotactoid glomerulopathy); and one patient with CLL had proliferative glomerulonephritis with subendothelial non organized monoclonal IgG3κ deposits (PGNMID).

Other renal lesions unrelated to the hematological disease were found in 12 patients (23%), including hypertensive nephropathy (n=7), diabetic nephropathy (n=2) and obesity-related focal segmental glomerulosclerosis (n=3).

Hematological response

All patients received clone-targeted therapy. Median interval from kidney biopsy to treatment initiation was 0.6 months. Among 21 patients with WM, only 1 was given steroids alone, whereas 20 received first-line alkylating-based regimens (associated with rituximab [n=3], or fludarabine [n=2]). Patients with CLL/SLL were treated with alkylating-based therapy

associated with rituximab (n=4) or fludarabine (n=2). Cyclophosphamide, doxorubicin, vincristine and prednisone (CHOP) was given to all patients with DLBCL, reinforced with rituximab in 6 cases. Other patients with NHL received various regimens, mostly based on rituximab, cyclophosphamide, vindesine and prednisone. The patient with MM received a combination of bortezomib, cyclophosphamide and dexamethasone.

Hematological response was evaluable after first-line chemotherapy in 50 patients. Of these, 28 had achieved hematological response, complete in 12 cases (DLBCL, n=7; WM, n=2; CLL/SLL, n=1; other NHL, n=2). Twenty-two patients required second-line treatment, because of refractory/relapsing disease (17 patients) or treatment-related toxicity (5 patients). Among 6 patients with DLBCL and available follow-up data, central nervous system relapse occurred in 2 cases, after 12 and 24 months from diagnosis respectively, and 1 patient had mediastinal relapse at 12 months. None of these patients experienced a kidney relapse, after a median follow-up of 18 (range, 12-48) months.

Twenty-four patients (46%) developed severe infections, including bacteremia (9 cases), pneumonitis (n=7), urinary tract infection (n=6), pneumocystis (n=1) and atypical mycobacterium (n=1) infections. Anemia and/or leukopenia ≥grade 3 occurred in 22 patients (42%). Others serious adverse events consisted of tumor lysis syndrome (n=2), deep vein thrombosis (n=3) and chemotherapy-induced hepatitis (n=1).

Renal and patient outcomes

Median follow-up was 31 (range, 15-70) months. At the time of censoring, 25 patients (48%) had achieved a renal response. Among the 27 patients (52%) without renal response, 21 progressed to ESRD after a median time of 30 (range, 14-64) months. Renal response appeared closely associated with the achievement of complete hematological response within the first 6 months: among 12 patients with complete hematological response, 11 achieved renal response (P=0.008). By univariate analysis (Table 3), factors influencing renal response were

hematological response (relative risk [RR]=2.96; confidence interval [95% CI]: 1.09-7.98, P=0.02), kidney enlargement (RR=3.26; 95% CI: 1.39-7.64, P=0.006), percentage of sclerotic glomeruli (RR=0.98; 95% CI: 0.94-0.99, P=0.03) and the presence of Ig-related nephropathy (RR=0.17; 95% CI: 0.05-0.29, P=0.005). The quality of hematological response was associated with increased probability of renal response (P=0.02): complete hematological response (RR=12.14; 95% CI: 1.57-94.1) and partial hematological response (RR=5.53; 95% CI: 1.09-7.98). In multivariate analysis, the presence of Ig-related nephropathy was the sole independent predictor of renal response (RR=0.16; 95% CI: 0.04-0.56, P=0.004). By Kaplan-Meier analysis, renal survival was significantly better in patients without Ig-associated renal lesions (P=0.006) (Figure 4).

Twenty patients (38%) died after a median of 21 (range, 2-144) months from diagnosis. Of these, 15 did not achieve a renal response, and 12 patients were on chronic hemodialysis. Causes of death were infections (n=6), hematological relapse/progression (n=6), cardiovascular disease (n=3) or unknown (n=5). Median overall survival differed significantly between renal responders and non-responders, respectively (97 versus 37 months, P=0.02) (Figure 4). By univariate analysis, factors influencing mortality were: age (RR=1.07; 95% CI: 1.03-1.12, P=0.002), hematological response (RR=0.10; 95% CI: 0.02-0.46, P=0.003), renal response (RR=0.10; 95% CI: 0.02-0.46, P=0.005) and serum creatinine at diagnosis (RR=0.97; 95% CI: 0.94-0.99, P=0.03). Hematological response was the sole independent factor influencing mortality by multivariate analysis (RR=0.13; 95% CI: 0.03-0.62, P=0.001).

Discussion

We herein report a large series of patients with biopsy-proven malignant B-cell renal infiltration, with particular focus on factors influencing renal and patient outcomes. This study indicates a previously under-recognized heterogeneity of renal presentation, depending on the type of the underlying B-cell lymphoproliferation and on the presence or not of renal lesions

induced by the deposition or precipitation of a monoclonal Ig secreted by the tumor. Most patients presented with invasive hematological disease and diffuse extranodal/extramedullary involvement in 42% of cases, whereas diagnosis was consistent with primary renal lymphoma in only 3 patients. These data confirm that primary extra-nodal renal lymphoma is exceptional, with an estimated incidence of 0.7% among all cases of extra-nodal lymphomas in the literature.[18,19] The apparent higher prevalence of this peculiar type of lymphoma in the present series could be due to the criteria used for patient selection, based on kidney biopsy. Whether some cases corresponded to systemic NHL seen at an early stage with unusual inaugural renal presentation remains unknown. In autopsy series, CLL/SLL was the most common B-cell lymphoma with renal tumoral infiltration. Leukemic infiltrates are sometimes present only within the perirenal soft tissue and renal capsule.[13,14] The low prevalence of CLL/SLL in the present series was probably due to the inclusion criteria used i.e. the presence of tubulo-interstitial or intravascular infiltration by lymphomatous cells. Patients with only renal capsule or perirenal fat lymphomatous cells infiltration were excluded. Our data further demonstrate that renal parenchymal infiltration by malignant plasma cells is an exceptional cause of kidney failure in MM. It was reported in only one patient of the present series, and in 2 out of a previous series of 190 patients with MM and biopsy-proven renal disease.[20]

In the whole cohort, renal symptoms were inaugural in 71% of patients, in whom renal pathological studies allowed the identification of the hematological disorder. AKI was the most common presenting symptom, found in 56% of patients at diagnosis, and severe (AKIN stage 3) in 35%, a finding consistent with previous series.[13,21] AKI, usually severe and without nephrotic-range proteinuria, was observed in most patients with high grade B-cell lymphoma, i.e. DLBCL. In 7/8 cases, it was associated with bilateral kidney enlargement secondary to the invasion of the renal interstitium by lymphoma cells, a finding usually considered as a major symptom of renal involvement in B-cell lymphomas. Bilateral renal enlargement was

previously reported in up to 87% of patients with AKI due to lymphomatous renal invasion, but the type of B-cell proliferation was not detailed in most studies.[17] By contrast, in other types of B-cell lymphomas, we found a lower prevalence of AKI at diagnosis. Most patients presented with nephrotic syndrome and only 9% displayed significant increase in renal size on imaging studies. These findings indicate that the diagnosis of renal malignant B-cell infiltration should not be excluded in the absence of suggestive radiological changes, that appear to reflect the burden of malignant infiltration in high grade lymphomas.

Malignant infiltration of the renal interstitium was diffuse in most cases, except in patients with CLL, half of whom showed focal nodular infiltrates. Of note, the pattern of tumor infiltration, either diffuse or focal, did not influence renal prognosis. In patients with lymphoma other than DLBCL, Ig-associated renal disease was frequent, reported in around half of patients of the present series, and seemed to strongly impact renal survival. As kidney biopsy is not widely performed in these patients, the prevalence of these lesions associated with renal B-cell lymphomatous infiltration remains poorly defined in the literature, and available data were established mostly in autopsy studies.[1,13,14] Different patterns of glomerular involvement have been described, including immunoglobulinic (AL) and secondary (AA) amyloidosis, membranous glomerulonephritis, or MPGN.[4,22,23] In our experience, the spectrum of glomerular lesions is wide with mostly AL amyloidosis or cryoglobulinemic glomerulonephritis. Tubulointerstitial disorders, such as cast nephropathy or light chain proximal tubulopathy, may also be associated with lymphomatous infiltration, as recently suggested in a series of 35 patients with monoclonal IgM secreting B-cell lymphoproliferative disorders.[11] The diagnosis of Ig-associated renal disease is sometimes challenging and requires complete pathological workup, including electron microscopy and detailed immunofluorescence studies with antibodies specific for IgG subclasses, to depict the nature of renal lesions in patients with B-

cell disorders and renal involvement. Studies are required to confirm the impact of these lesions on renal outcomes in patients with lymphomatous parenchymal infiltration.

The specific effect of renal parenchymal infiltration on overall and renal survival in B-cell lymphoproliferative disorders remains poorly described. Previous studies have described the deleterious impact of AKI on patient survival in various high-grade hematological malignancies, but without specific focus on B-cell lymphomas.[21,24] Our results indicate that the prognosis of renal B-cell lymphomatous infiltration is poor, with a five-year overall survival of 60%. In the present cohort, patients who achieved renal response had significantly higher survival rates than those who did not, suggesting that improvement of renal function should be regarded as an important clinical issue. Hematological response was a major determinant of renal response, highlighting the need for urgent introduction of chemotherapy adapted to the infiltrating clone.[25] Of note, B-cell lymphomas appeared to be associated with different renal and patient outcomes, depending on the rate of clonal proliferation. Patients with DLBCL, who almost invariably exhibited enlarged kidneys, usually achieved complete renal response with chemotherapy, according to previous series.[26] It has been hypothesized that diffuse interstitial infiltration increases intra-renal pressure and modifies renal hemodynamics, leading to reversible ischemia.[16,17] Of note, whereas none of DLBCL patients of the present series had a kidney relapse, 3/8 patients died of disease relapse or progression, including central nervous system relapse in 2 cases. The high incidence of central nervous system disease recurrence in patients with DLBCL and kidney involvement has been reported in 20% in the literature,[27] leading to fatal outcome in most cases. These data underline the need for systematic central nervous system evaluation at diagnosis and during follow-up in DLBCL.

By contrast, in other types of B-cell lymphoma, renal disease appears to be more insidious and heterogeneous, with a high prevalence of nonspecific degenerative lesions and glomerular or tubular lesions induced by the secretion of monoclonal Ig by the tumor.[11,28,29]

Apart from hematological response, the percentage of sclerotic glomeruli and the presence monoclonal Ig-related renal lesions were associated with poor renal outcome. This indicates that renal histological studies should be considered systematically, not only for diagnostic assessment, but also for prognostic evaluation of renal disease.

Our study has several limitations. First, the study population was heterogeneous, with different types of hematological malignancies associated with distinct natural histories and responses to chemotherapy. Second, our cohort was recruited over a prolonged time period, during which treatment regimens changed, particularly with the introduction of rituximab in the most recent cases. Finally, all cases are Caucasian patients.

In conclusion, the clinicopathological spectrum of renal lymphomatous infiltration depends on the nature of the underlying B-cell clone. In DLBCL, AKI and kidney enlargement are characteristic features that should prompt rapid lymph node biopsy to confirm diagnosis. Other types of B-cell lymphomatous infiltration manifest with various renal symptoms, reflecting the high frequency of associated Ig-related nephropathy and kidney biopsy is required for early diagnostic and prognostic assessment.

Materials and methods

Study participants

Fifty-two Caucasian patients referred to 8 French Nephrology departments between 1991 and 2016 were retrospectively studied. Inclusion criteria were: (1) biopsy-proven infiltration of renal parenchyma by malignant B-cells ; (2) estimated glomerular filtration rate (eGFR) ≤60 mL/min/1.73m^2; (3) and/or proteinuria >0.5 g/day. Patients with prior severe chronic kidney disease (CKD) (eGFR <15mL/min/1.73 m^2) were excluded. This study was performed in accordance with the Declaration of Helsinki and received approval by the local ethics committee.

Clinical data

Acute kidney injury was defined according to the Acute Kidney Injury Network (AKIN) criteria.[30] eGFR was calculated using the CKD-EPI (Chronic Kidney Disease Epidemiology Collaboration equation.[31] CKD was defined based on the Kidney Disease Outcomes Quality Initiative classification.[32]

Renal response was assessed using the following definitions: complete response by achievement of eGFR >60 mL/min/1.73m^2 and proteinuria <0.5 g/day; partial response by a ≥50% increase in eGFR or reduction in proteinuria by 50% with stable renal function for patients with baseline eGFR >60 mL/min/1.73m^2. Patients without criteria for renal response, including those with progressive CKD or who reached end-stage renal disease (ESRD), were considered as non-renal responders.

Hematological and immunological studies

Bone marrow smears or biopsies were performed in all patients. Diagnosis of lymphoproliferative disease was established according to the 2016 revision of the World Health Organization classification.[33] All patients underwent diagnostic imaging with computed

tomography scan and/or fluorine-18-fluorodeoxyglucose positron emission tomography. Detection of serum and urine monoclonal immunoglobulin was performed in all patients using electrophoresis and immunoelectrophoresis/immunofixation.

The revised international prognostic index (R-IPI),[34] the International Prognostic Scoring System for WM (ISSWM)[35] and the Binet classification[36] were used in patients with B-cell NHL, WM and CLL respectively. Hematological response was defined according to the international response criteria for B-cell lymphoproliferative disorders.[37-40]

Pathological studies

All kidney biopsy samples were processed for light microscopy, immunofluorescence (IF) and immunohistochemistry. Sections were systematically stained with Congo red and examined under polarized light. For IF, 3 μm cryostat sections were stained with fluorescein isothiocyanate (FITC) conjugates specific for γ, μ, α immunoglobulin heavy chain, κ and λ light chain (Dako, Glostrup, Denmark) and C3, C1q (MorphosysAbD, Düsseldorf, Germany). Immunophenotyping of bone marrow and renal cellular infiltration was performed by immunohistochemistry using conjugates specific for CD10 (Novocastra, Newcastle, UK), CD5 (Becton-Dickinson, San Jose, CA, USA), anti-CD20, anti-CD19, CD3 (Dakopatts, Glostrup, Denmark), CD79a (Thermo, Fisher scientists), CD138 and CD23 (Ventana, Roche). The extent of tumoral infiltration of renal parenchyma was graded diffuse when occupied ≥50% of the renal cortex surface, or focal. In 40 cases, ultrathin sections were processed for electron microscopy and examined under a JEOL JEM-1010 electron microscope (Tokyo, Japan), as previously described.[41]

Statistical analysis

Quantitative data was expressed as means ± standard deviation or median with range. Comparisons were conducted using t-test or Wilcoxon test for normally and non-normally distributed continuous variables, respectively. Comparisons for categorical variables were

performed using Chi-2 or Fisher exact tests. Patient survival was analysed by the Kaplan Meier method using the log-rank test for univariate analysis. Risk prediction model established by Cox proportional hazard model was used to analyse factors influencing renal response and mortality. Hazard ratio and its 95% confidence interval were presented. Statistical significance was assumed at $P < 0.05$. Statistical analyses were carried out using the SAS software version 9.3 (SAS Inc., Cary, NC, USA).

Disclosure

All the authors declared no competing interests.

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Figure legends

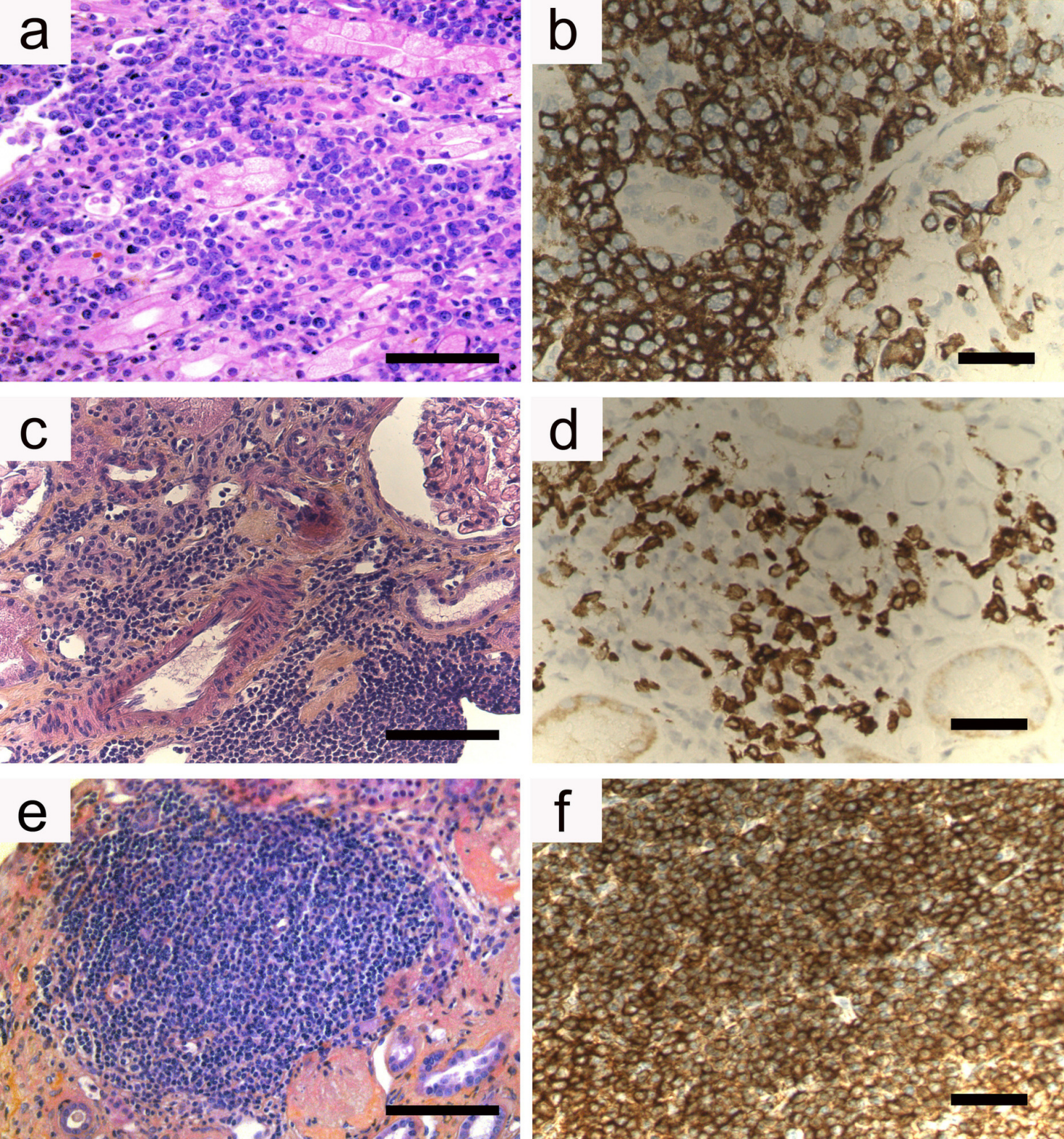
Figure 1. Patterns of renal parenchymal infiltration. (a, b) Patient with diffuse large B-cell lymphoma. (a) Diffuse tumoral infiltration of the kidney by large atypical lymphocytes (Hematoxylin and eosin staining, original magnification ×200) positive for CD20 (b) by immunohistochemistry analysis (original magnification ×400). (c, d) Patient with Waldenström macroglobulinemia. (c) Widespread infiltration of the kidney by lymphoplasmacytic cells (Hematoxylin and eosin staining, original magnification ×200). The infiltrating tumoral cells were positive for CD79A (d) and CD20 (not shown) by immunohistochemistry analysis (original magnification ×400). (e, f) Patient with chronic lymphocytic leukemia. (e) Focal nodular tumoral infiltration of the subcapsular region by small lymphocytes (Hematoxylin and eosin staining, original magnification ×200) positive for CD20 (f) by immunohistochemistry analysis (original magnification ×400). Bar=50 µm.

Figure 2. Intravascular large B-cell lymphoma. (a, b) Light microscopy showing lymphomatous infiltration (arrows) of peritubular capillaries. (a) Hematoxylin and eosin staining, original magnification ×400, bar=50 µm. (b) Toluidine blue staining, original magnification ×1000, bar=25 µm. (c) Immunohistochemistry analysis (original magnification ×200). Lymphoid cells infiltrating peritubular and glomerular capillaries were positive for CD20, bar=50 µm. (d) Electron microscopy (original magnification ×3000). Tumoral lymphoid cells are characterized by nuclear irregularities, inconspicuous nucleoli and scant cytoplasm. Bar=2 µm.

Figure 3. Monotypic plasma cell interstitial nephritis. (a, b) Light microscopy, original magnification ×400. (a) Section of renal cortex showing tubulointerstitial nephritis with cell infiltrate mostly consisted of plasma cell (Hematoxylin and eosin staining). (b) Glomerulus with Congo-red positive deposits stained with anti-lambda light-chain antibody by immunofluorescence analysis (not shown) consistent with associated AL-amyloidosis (Congo-

red staining). (c-e) Immunohistochemistry analysis, original magnification ×200. Tumoral infiltrating cells were positive for CD138 (c) and lambda light-chain (d), and negative for kappa light-chain (e). Bar=50 µm.

Figure 4. Kaplan-Meier survival analysis. (a) Overall survival curves according to renal response status. Patient survival was significantly better in renal responders compared to non-renal responders (P=0.01). (b) Renal survival curves for patients with and without immunoglobulin associated renal lesions. Renal survival was significantly better in patients without immunoglobulin associated renal lesions (P=0.006).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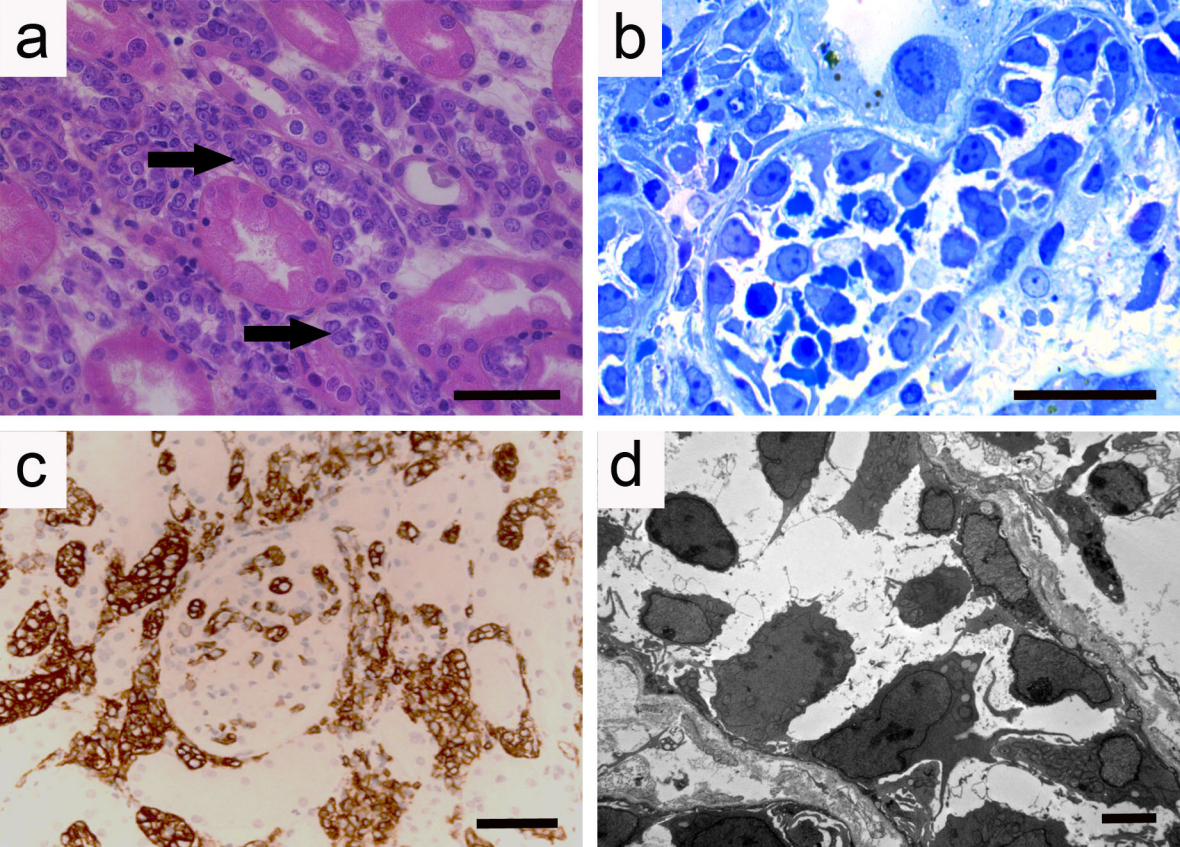
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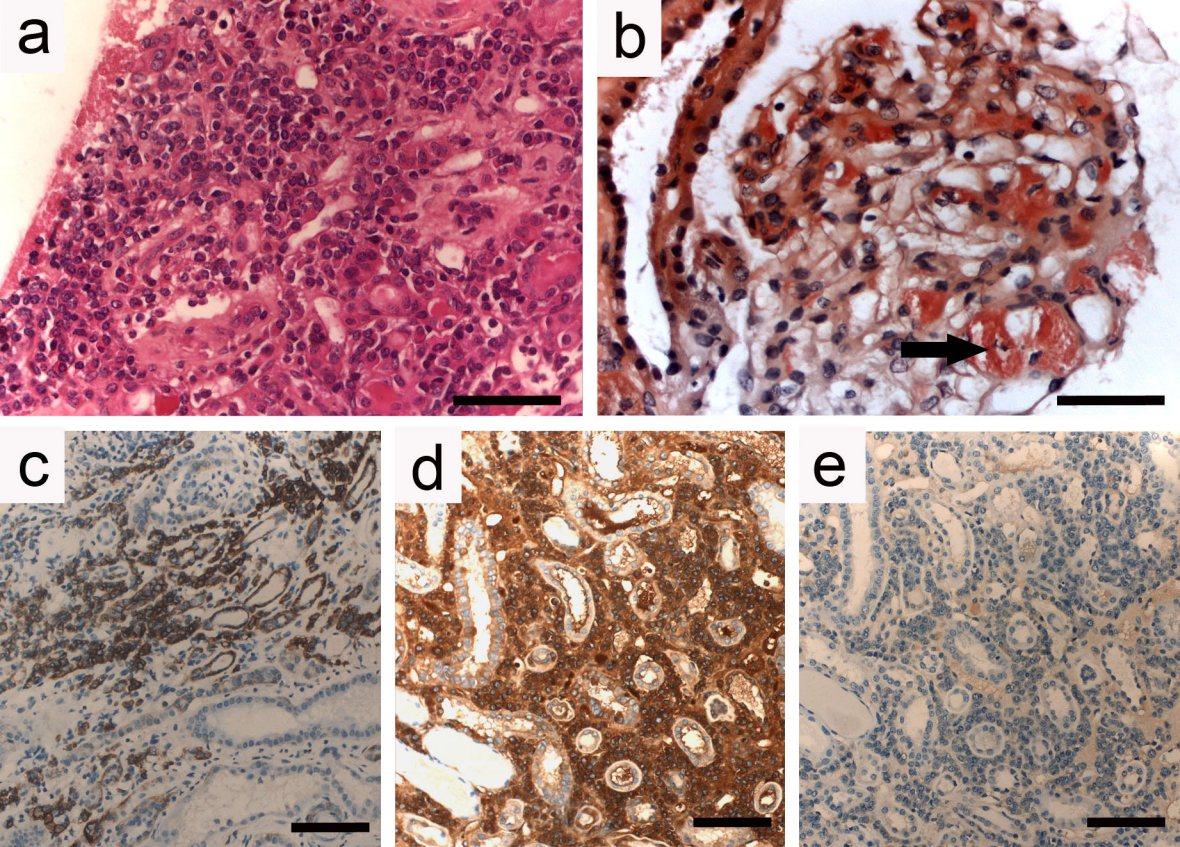
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Table 1. Baseline characteristics according to the type of B-cell disorder

	WM *(n=21)*	CLL *(n=11)*	Other low grade lymphoma *(n=11)*	DLBCL *(n=8)*	Myeloma *(n=1)*	All *(n=52)*
Demographic characteristics						
Age, *years*	72 [49-89]	68 [45-78]	69 [38-90]	52 [17-72]	65	65 [17-90]
Male/female ratio	0.9	4.5	1.2	1.7	1	1.5
Comorbid conditions						
Hypertension, *n (%)*	6 (29)	3 (27)	2 (18)	0	0	11 (21)
Diabetes mellitus, *n (%)*	4 (19)	2 (18)	2 (18)	0	0	8 (15)
Pre-existing CKD, *n (%)*	11 (52)	6 (55)	3 (27)	0*	0	20 (38)
Clinical findings						
Hypertension, *n (%)*	7 (33)	3 (27)	4 (36)	1 (13)	0	15 (29)
Oliguria, *n (%)*	2 (10)	1 (9)	2 (18)	4 (50)*	0	9 (17)
Laboratory findings						
Serum creatinine, *µmol/L*	176 [85-634]	300 [76-1184]	224 [120-1051]	183 [61-771]	180	215 [56-1184]
Acute kidney injury, *n (%)*	9 (43)	5 (45)	8 (73)	6 (75)	1	29 (56)
AKIN score 3, *n (%)*	4 (19)	5 (45)	5 (45)	4 (50)	0	18 (35)
Hematuria, *n (%)*	11 (52)	7 (64)	8 (73)	3 (37.5)	1	30 (58)
Proteinuria ≥1g/day, *n (%)*	17 (81)	6 (55)	8 (73)	3 (37.5)	1	35 (67)
Nephrotic syndrome, *n (%)*	7 (33)	3 (27)	6 (55)	1 (12.5)	1	18 (35)
Serum monoclonal Ig, *n (%)*	21 (100)	8 (73)	7 (64)	1 (12.5)*	1	38 (73)
IgM/IgG/IgA	21/0/0	2/5/1	2/4/1	1/0/0	0/0/1	26/9/3
Bence Jones proteinuria, *n (%)*	14 (67)	6 (55)	6 (55)	1 (12.5)*	1	28 (54)
Kappa/lambda	12/2	3/3	4/2	1/0	0/1	20/8
Morphological abnormalities						
Kidney enlargement, *n (%)***	1 (5)	0	3 (27)	7 (88)*	0	11 (21)
Extrarenal involvement						
Lymph nodes, *n (%)*	10 (48)	7 (64)	7 (64)	7 (87.5)	0	31 (60)
Extranodal/extramedullary, *n (%)*	5 (24)	7 (64)	4 (36)	6 (75)	0	22 (42)
International prognostic score						
ISSWM >2, *n (%)*	16 (76)	-	-	-	-	-
Binet stage C, *n (%)*	-	7 (64)	-	-	-	-
R-IPI >2, *n (%)*	-	-	-	6 (75)	-	-

Abbreviations: AKIN, Acute Kidney Injury Network; CKD, chronic kidney disease; CLL, chronic lymphocytic leukemia; DLBCL, diffuse large B-cell lymphoma; Ig, immunoglobulin; ISSWM, International Prognostic Scoring System for Waldenström macroglobulinemia; R-IPI, revised International Prognostic Index; WM, Waldenström macroglobulinemia.

*P<0.05, when comparing DLBCL to other types of lymphoma.

** Kidney enlargement was significantly more frequent in DLBCL versus WM (p<0.0001), CLL (p=0.0002) and other low grade lymphoma (p=0.02).

Table 2. Renal biopsy findings

	WM *(n=21)*	CLL *(n=11)*	Other low grade lymphoma *(n=11)*	DLBCL *(n=8)*	Myeloma *(n=1)*	All *(n=52)*
Tumoral infiltrate, *n (%)*						
Interstitium						
Diffuse	14 (67)	8 (73)	10 (91)	7 (87.5)	1	40 (77)
Focal	7 (33)	3 (27)	1 (9)	0	0	11 (21)
Tubule	1 (5)	0	0	4 (50) *	0	5 (10)
Peritubular capillaries	1 (5)	0	0	4 (50) *	0	5 (10)
Glomerular capillaries	1 (5)	2 (18)	2 (18)	6 (75) *	0	11 (21)
Mean percentage of sclerotic glomeruli	20	18	27	2.5*	20	19
Related to hematological disease, *n (%)*	11 (52)	5 (45)	3 (27)	0*	1	20 (38)
AL amyloidosis	5 (24)	0	0	0	1	6 (12)
Cryoglobulinemic glomerulonephritis	1 (5)	1 (9)	1 (9)	0	0	3 (6)
Cast nephropathy	2 (10)	1 (9)	0	0	0	3 (6)
MIDD	1 (5)	0	1 (9)	0	0	2 (4)
GOMMID	0	2 (18)	0	0	0	2 (4)
Light chain proximal tubulopathy	1 (5)	0	0	0	0	1 (2)
PGNMID	0	1 (9)	0	0	0	1 (2)
Membranous glomerulonephritis**	0	0	1 (9)	0	0	1 (2)
Thrombotic microangiopathy	1 (5)	0	0	0	0	1 (2)
Unrelated to hematological disease, *n (%)*	6 (29)	3 (27)	3 (27)	0*	0	12 (23)
Hypertensive nephropathy	3 (14)	2 (18)	2 (18)	0	0	7 (13)
Diabetic nephropathy	2 (10)	0	0	0	0	2 (4)
Obesity-related FSG	1 (5)	1 (9)	1 (9)	0	0	3 (6)

Abbreviations: CLL, chronic lymphocytic leukemia; DLBCL, diffuse large B-cell lymphoma; FSG, focal-segmental glomerulosclerosis; GOMMID, glomerulonephritis with organized microtubular monoclonal immunoglobulin deposits (immunotactoid glomerulopathy); MIDD, monoclonal immunoglobulin deposition disease; PGNMID, proliferative glomerulonephritis with monoclonal immunoglobulin deposits; WM, Waldenström macroglobulinemia.

*P<0.05, when comparing DLBCL to other types of lymphoma.

**Patient with marginal zone lymphoma without associated hepatitis C or Sjogren syndrome.

Table 3. Univariate and multivariate analysis of factors influencing renal response

	Univariate analysis			Multivariate analysis		
Parameters	**HR**	**95% CI**	**P value**	**HR**	**95% CI**	**P value**
Clinical findings						
Age (years)	1.00	0.98-1.04	0.7			
Urine protein excretion >1g/day	0.53	0.24-1.20	0.1			
eGFR (ml/min/1.73 m^2)	1.00	0.99-1.02	0.9			
AKIN stage 3	0.76	0.3-1.93	0.6			
Chronic kidney disease	0.43	0.17-1.12	0.08			
Chronic kidney disease stage ≥3	0.38	0.13-1.16	0.08			
Radiological findings						
Kidney enlargement	3.26	1.39-7.64	**0.006**	2.46	0.96-6.3	0.06
Pathological findings						
Interstitial infiltrate			0.4			
Diffuse	1					
Focal	0.62	0.21-1.83				
Percentage sclerotic glomeruli	0.98	0.94-0.99	**0.04**			
Ig-associated nephropathy	0.17	0.05-0.29	**0.004**	0.16	0.04-0.56	**0.004**
Underlying B-cell clone			0.09			
Waldenström macroglobulinemia	1					
Chronic lymphocytic leukemia	0.34	0.07-1.60				
DLBCL	3.77	1.25-11.43				
Mantle cell lymphoma	0.95	0.20-4.48				
Follicular lymphoma	0.56	0.12-2.65				
Marginal zone lymphoma	1.65	0.2-13.8				
Myeloma	-	-				
Hematological response			**0.02**	2.65	0.96-7.34	0.06
No	1					
Partial	5.53	1.09-7.98				
Complete	12.14	1.57-94.1				

Abbreviations: AKIN, acute kidney injury network; CI, confidence interval; DLBCL, diffuse large B-cell lymphoma; eGFR, estimated glomerular filtration rate; HR, hazard ratio; Ig, immunoglobulin.