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Clinical Presentation and Pathology Spectrum of Kidney Damage in Non-Hodgkin Lymphoma/Leukemia and Lymphoplasmacytic Lymphomas

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Abstract

Kidney damage in non-Hodgkin lymphoma/leukemia (NHL/CLL) and lymphoplasmacytic lymphomas (LPCL) are caused by several mechanisms: tumor mass localization; clonal cell expansion; hormones, cytokines and growth factors secretion; metabolic, electrolyte and coagulation disturbances; deposition of paraproteins and treatment complications. Symptoms of kidney damage may dominate and even preclude overt NHL/CLL or LPCL, and only renal pathology findings give the clue to the diagnosis. We aimed to evaluate clinical presentation and pathology of kidney damage in patients with NHL/CLL or LPCL. Using electronic database and purposely designed chart, we searched data for 158 patients with lymphoproliferative disorders (LPD) and pathology proven kidney lesions. Patients with multiple myeloma, Hodgkin's lymphoma, Castleman disease, "primary" AL amyloidosis and "primary" light chain deposition disease were excluded from further analysis. Study group consisted of 24 patients, 14 (58.3%) male and 10 (41.7%) female, median age 67 (17;76) years. 16 patients (66.6%) were diagnosed with NHL/CLL, 7 patients (29.1%) with Waldenström's Macroglobulinemia (WM) and 1 (4.1%) with Franklin's disease (FD). 10 (41.7%) of patients presented with nephrotic syndrome (NS), 17 (70.8%)–with impaired kidney function, and 6 (25.2%) with both NS and renal dysfunction. By pathology glomerulonephritis (GN) was found in 11 (45.8%) of patients, in 4 cases GN pattern was associated with monoclonal paraproteins, and in 7 cases GN was considered to be paraneoplastic. Interstitial nephritis was seen in 10 (41.6%) patients, in 8 of them due to specific lymphoid infiltration; and amyloidosis complicated only 3 (12.5%) cases. Patients with NHL/CLL or LPCL, presenting with renal abnormalities, show variety of pathology patterns hardly predictable on clinical basis. Most often in our patient series was specific lymphoid interstitial infiltration and paraneoplastic glomerulonephritis with MN and MPGN patterns. In many cases of NS and/or acute kidney injury (AKI) renal biopsy was crucial for the diagnosis of NHL/CLL and LPCL.

Keywords: Kidney biopsy; Lymphoma; Nephropathy

Introduction

Kidneys are affected in patients with NHL/CLL and LPCL not that often as in multiple myeloma, however, kidney damage is represented with a broad spectrum of clinical and pathology variants. Renal involvement is defined by several mechanisms (Table 1) tumor mass localization; clonal cell expansion; hormones, cytokines and growth factors secretion; metabolic, electrolyte and coagulation disturbances; infectious, drug-induced and radiation complications etc., affecting urinary tract, renal arteries and veins and all parenchymal compartments: intra-renal vasculature, glomeruli, tubules and interstitial space, sometimes simultaneously. Rarely kidney damage may be caused by deposition of secreted paraproteins, including organized (fibrils, microtubules), and non-organized deposits of monoclonal immunoglobulin's or fragments thereof [1-6].

Pre-renal acute kidney injury	
Hyperviscosity syndrome	
Specific infiltration	Interstitial infiltration
	Intraglomerular lymphoma
Paraneoplastic glomerulonephritis	Membranous nephropathy
	Membranoproliferative glomerulonephritis
	Minimal change disease/Focal segmental glomerulosclerosis

Metabolic nephropathies	Tumor-lysis syndrome (uric acid/phosphate nephropathy)	
Thrombotic damages	Renal vein thrombosis	
	Thrombotic microangiopathy	
Urinary tract obstruction	Compression with lymph nodes	
	Retroperitoneal fibrosis	
Infectious complications	Sepsis	
	Urinary tract infection	
	AA amyloidosis caused by chronic infections and inflammation	
Radiation-induced nephritis		
Drug-induced nephritis	Minimal change disease	
	Membranous nephropathy	
	Interstitial nephritis	
Paraprotein deposition	Organized paraprotein deposits	Cryoglobulinemic glomerulonephritis
		Glomerulonephritis with organized microtubular monoclonal deposits (Immunotactoid Glomerulonephritis)
		Al and AH amyloidosis
	Non-organized paraprotein deposition	Glomerulonephritis with monoclonal intracapillary IgM deposits
		Proliferative glomerulonephritis with monoclonal immunoglobulin deposits (Nasr disease)
		Monoclonal immunoglobulin deposition disease

Table 1: Mechanisms and patterns of kidney damage in non-Hodgkin lymphoma/leukemia and lymphoplasmacytic lymphomas.

Clinical presentation of renal involvement in patients with NHL/CLL and LPCL include AKI, NS, proteinuria and/or hematuria, arterial hypertension or chronic kidney disease (CKD). Differential diagnostics is the major challenge, often, but not obligatory demanding pathology evaluation. Pre-renal AKI, tumor-lysis syndrome, or urinary tract obstruction by lymph nodes can be diagnosed on clinical basis, but many conditions cannot be differentiated in solely clinical setting. Importantly, symptoms of kidney damage may dominate and even preclude overt NHL/CLL or LPCL, and only pathology findings give the clue to the diagnosis.

Pathology patterns (Table 1) include interstitial or glomerular specific infiltration; cryoglobulinemic GN (CryoGN); proliferative (PGNMID) and non-proliferative GN with monoclonal immunoglobulin deposits; immunotactoid (GOMMID) and fibrillary GN; paraneoplastic GN - mostly membranous nephropathy (MN) and membranoproliferative GN (MPGN); AL/AH amyloidosis, and even AA amyloidosis [4-13]. In turn, MN and MPGN are known to be often secondary to lymphomas, and immunotactoid and fibrillary GN, defined by electron microscopy (EM), may present like MN and MPGN by light microscopy (LM) evaluation [14-16].

Given the serious prognosis for NHL/CLL and LPCL as such, and for kidney damage in this setting in particular, and also the fact that overall and kidney survival depend to the considerable extent on early diagnostics, we aimed to evaluate the clinical presentation and the pathology patterns in patients, admitted to nephrology unit and diagnosed with NHL/CLL and LPCL.

Materials and Methods

Patient's population

In this retrospective study from a single center, using electronic database with 10277 records for primary admissions over last 21 years (1994-2015), and purposely designed chart, we searched and analyzed data for 315 patients (3.0%) with LPD and plasma cell dyscrasias. We found 158 cases (50.1%) with pathology proven diagnosis. Patients with multiple myeloma, Hodgkin's lymphoma, Castleman disease, "primary" AL amyloidosis and "primary" light chain deposition disease were excluded from further analysis. 24 patients with NHL/CLL and LPCL and biopsy proven kidney lesions were carefully evaluated (Figure 1).

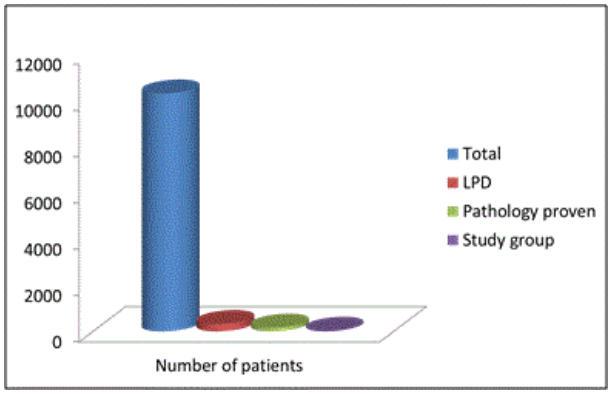

Figure 1: Proportion of study group versus total patient's population, all patients with lymphoproliferative disorders and patients with pathology-proven LPD.

Main diagnosis

Diagnosis of NHL/CLL and LPCL was determined in collaboration with hematologist according to WHO Classification of Tumours of Haematopoietic and Lymphoid Tissues [17].

Work-up

Work-up, beyond routine, included serum and urine immunoelectrophoresis; peripheral blood immunophenotyping; abdomen, kidneys and peripheral lymph nodes ultrasound; skeletal X-ray; chest and abdomen CT; bone marrow aspiration and/or biopsy; and/or lymph node biopsy with light microscopy and immunohistochemistry; and kidney biopsy.

Kidney biopsy

Indications for kidney biopsy included NS, proteinuria (>0.3 g/24 h) and/or hematuria and/or decreased kidney function (in cases with ruled out intra- and extra-renal tumor masses, urinary tract obstruction, coagulation, electrolyte and metabolic disturbances and sepsis). Kidney core biopsy was taken with BARD-Magnum biopsy guidance facility and evaluated by one pathologist. In selected cases second opinion and/or re-processing and re-evaluation was requested from external pathologists. Obtained specimens were divided into two or three parts and processed for LM, immunofluorescence (IF) or immunhistochemistry, and, in selected cases, EM. Formalin fixed/paraffin embedded sections for LM were stained with hematoxylin and eosin, Masson's trichrome, periodic acid-Shiff and Congo red. Unfixed cryo-sections for IF were routinely stained for IgA, IgG, IgM, C3, C1q, kappa and lamda light chains and fibrinogen. In selected cases immunofluorescence on formalin fixed/paraffin embedded sections with FITC-conjugated anti IgA, IgG, IgM, C1q, C3, fibrinogen, λ and κ light chains antibodies, and immunoperoxidase staining for amyloid A-protein was performed. Also in 5 (20.8%) cases Toluidune blue stained semi-thick sections were examined and 1 glomerulus was identified for EM study (by external pathologist).

Results and Discussion

Study group comprised 15.1% of all cases of LPD with pathology proven kidney damage, and included 24 patients, 14 (58.3%) male and 10 (41.7%) female, median age 67 (17;76) years.

Clinical diagnosis and presentation

16 patients (66.6%) were diagnosed with NHL/CLL, 7 patients (29.1%) with Waldenström's Macroglobulinemia (WM) and 1 (4.1%) with Franklin's disease (FD). In 11 cases diagnosis of NHL/CLL or LPCL was primarily established in the nephrology unite.

10 (41.7%) patients presented with NS; 17 (70.8%) had impaired kidney function at the time of biopsy; and 6 (25.2%) presented with both NS and renal dysfunction. 12 (50%) patients were diagnosed with CKD stage 3-5, and 5 (20.8%) patients had AKI, totally 4 (16.6%) of them required urgent dialysis at presentation (Figure 2).

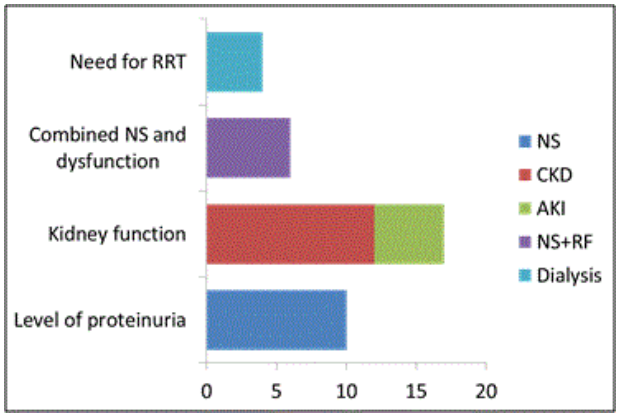

Figure 2: Clinical presentation in the study group.

Pathology findings

Pathology data (Table 2) showed that kidney damage in patients with NHL/CLL and LPCL presented with 11 different patterns described in the literature [4-13]. Glomerulonephritis comprised almost half of cases and was found in 11 (45.8%) of patients, in 4 cases GN was associated with monoclonal paraproteins, and in 7 cases was considered to be paraneoplastic. Interstitial nephritis was found in 10 (41.6%) patients, with 8 of them due to specific lymphoid infiltration, and amyloidosis complicated only 3 (12.5%) cases.

Pathology pattern	**N**
Glomerulonephritis	**11**
Associated with monoclonal immunoglobulin's	***4***
Cryoglobulinemic glomerulonephritis	1
Glomerulonephritis with monoclonal IgM deposits	3
Paraneoplastic	***7***
Membranoproliferative glomerulonephritis	2
Membranous nephropathy	3

Focal segmental glomerulosclerosis	1
Diffuse glomerulosclerosis	1
Amyloidosis	**3**
Immunoglobulin related	***2***
AL amyloidosis	1
AH amyloidosis	1
Non-immunoglobulin related	1
AA amyloidosis	1
Interstitial nephritis	**10**
Specific interstitial infiltration	***8***
Drug-induced interstitial nephritis	***2***

Table 2: Kidney pathology data in the study group.

Clinical and pathology correlations

As it is shown in the Table 3, some pathology patterns were strictly associated with the particular diagnosis, but on the other hand same pathology findings could be seen in different clinical setting and vice versa.

Pathology/Main diagnosis	NHL/CLL	WM	FD
Cryoglobulinemic glomerulonephritis		1	
Glomerulonephritis with monoclonal IgM deposits		3	
Membranoproliferative glomerulonephritis	2		
Membranous nephropathy	2	1	
Focal segmental glomerulosclerosis		1	
Diffuse glomerulosclerosis	1		
AL amyloidosis		1	
AH amyloidosis			1
AA amyloidosis	1		
Specific interstitial infiltration	8		
Drug-induced interstitial nephritis	2		

Table 3: Diagnosis and pathology correlations.

Monoclonal immunoglobulin–associated glomerulonephritis

A case of cryoglobulinemic glomerulonephritis, as well as 3 cases of glomerulonephritis with monoclonal IgM deposits were not surprisingly found in patients with WM (Figures 3 and 4). In all four cases patients were referred to our unit with NS and only kidney biopsy findings lead to further specifically directed work-up and to the final diagnosis.

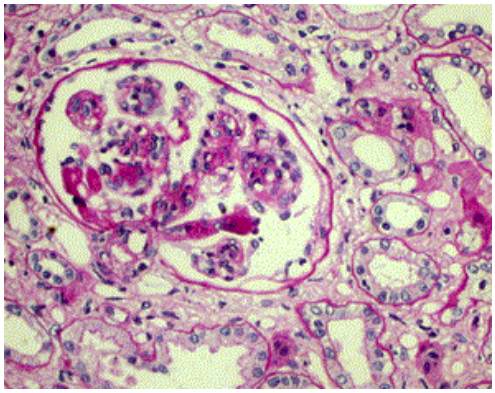

Figure 3: Cryoglobulinemc GN, PAS x 250.

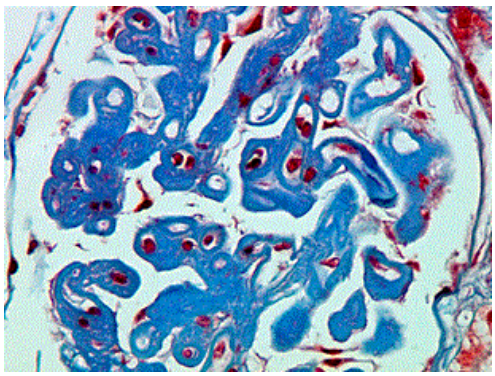

Figure 4: GN with IgM deposits, Masson x 400.

Paraneoplastic glomerulonephritis

Membranoproliferative glomerulonephritis was found in 2 patients with MALT lymphoma, membranous nephropathy was revealed in 2 patients with MALT lymphoma (Figures 5 and 6) and in 1 patient with WM. The single case of focal segmental glomerulosclerosis was also seen in WM. As both MPGN and MN are known to be “secondary” to NHL and these LM and IF patterns may represent fibrillary GN, we can speculate, that our 4 patients with MALT lymphoma had in fact fibrillary GN. Unfortunately, we were not able to prove this by EM in that particular cases. Again, in two of these patients only kidney biopsy, performed because of NS, lead to diagnostic search for the possible cause of “secondary” MN/MPGN and allowed to diagnose gastric and peripheral lymph nodes MALT lymphomas.

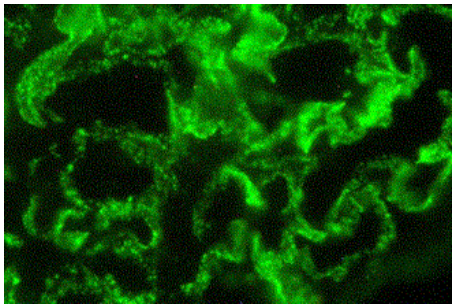

Figure 5: Membranous nephropathy, IF IgGx400.

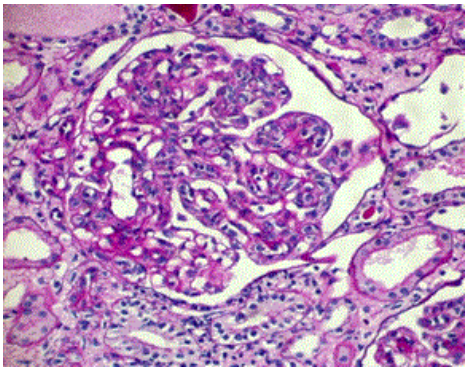

Figure 6: MPGN, PASx250.

Amyloidosis

AL amyloidosis was found in one case of WM, AH amyloidosis was seen in a patient with FD, and AA amyloidosis was the complication of Burkitt lymphoma with spinal chord damage and bed sores. All these variants are rare, interestingly that diagnosis of FD was again established on the basis of kidney pathology - renal AH amyloidosis in a patient with moderate proteinuria gave a clue to the diagnosis, which was confirmed by bone marrow biopsy and immunelectrophoresis of serum and urine proteins (Figures 7 and 8).

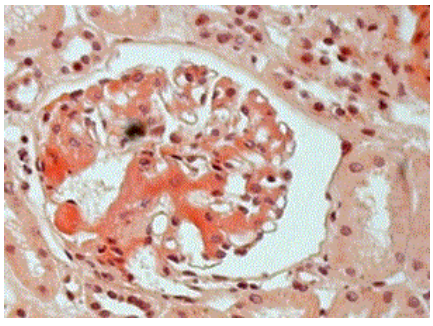

Figure 7: AH amyloidosis, Congo red x250.

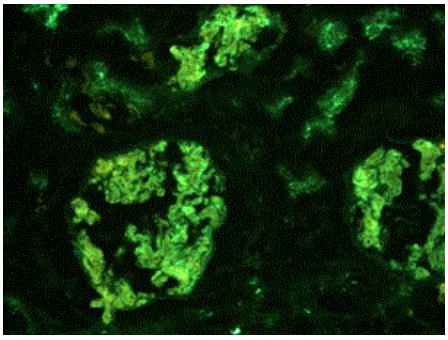

Figure 8: AH amyloidosis, IF IgGx250.

Interstitial lymphoid infiltration

NCL/CLL - mostly specific lymphoid infiltration was found in 8 cases, all in patients with NHL/CLL-mostly follicular lymphoma and small lymphocytic lymphoma, and only in one patient with acute lymphoblastic T-cell leukemia (Figures 9 and 10).

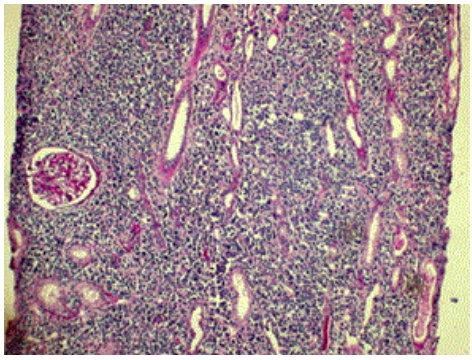

Figure 9: Lymphoid infiltration, PAS x 100.

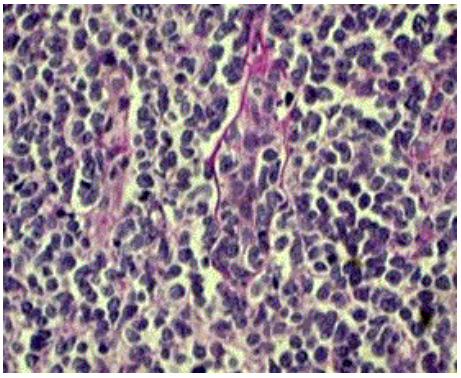

Figure 10: Lymphoid infiltration, PAS x 400.

Conclusion

Our retrospective single-center study of 24 patients with pathology-proven kidney damage showed, that patients with non-Hodgkin lymphomas and lymphoplasmacytic lymphomas, presenting with renal abnormalities, show variety of pathology patterns, hardly predictable on clinical basis. Most often in our patient series turned to be specific lymphoid interstitial infiltration and paraneoplastic glomerulonephritis with MN and MPGN patterns. In many cases of nephrotic syndrome and/or acute kidney injury, renal biopsy, precluded or followed by scrutinous hematological work-up is crucial for the diagnosis of NHL/CLL and LPCL.

Conflict of Interest

Nothing to declare

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