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A Diverse Spectrum of Immune Complex– and Complement-Mediated Kidney Diseases Is Associated With Mantle Cell Lymphoma

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Introduction: There are limited reports on kidney biopsy findings in patients with mantle cell lymphoma (MCL).

Methods: We initiated a multi-institutional, retrospective review of kidney biopsy findings in patients with active and treated MCL.

Results: A total of 30 patients with MCL and kidney biopsies were identified, with a median age of 67 (range 48–87) years, 73% of whom were men. A total of 20 patients had active MCL at the time of biopsy, of whom 14 (70%) presented with acute kidney injury (AKI), proteinuria and/or hematuria, and biopsy findings potentially attributable to lymphoma. Of the 14, 11 had immune complex (IC) or complement-mediated (C3) disease including proliferative glomerulonephritis (GN) with monotypic Ig deposits (PGNMID [2]), C3GN, (2), secondary membranous nephropathy (MN [3]), tubular basement membrane (TBM) deposits (2), and modest lupus-like GN (2). Lymphomatous infiltration was present in 8 of the 20 patients, 5 with coincident IC or C3 lesions. A total of 6 patients with available follow-up were treated for MCL, all with clinical remission of GN (2 PGNMID, 2 C3GN, and 2 MN).

Conclusion: MCL is associated with diverse monoclonal and polyclonal glomerular and extra-glomerular IC and C3 disease. For patients with active MCL and kidney dysfunction requiring biopsy, 70% had findings due or potentially due to lymphoma, including 55% with IC or C3 disease and 40% had lymphomatous kidney infiltration. IC and C3GN in the setting of active MCL was responsive to lymphoma-directed therapy.

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The increasing recognition of kidney disease in patients with lymphoproliferative and plasma cell disorders has led to a recent surge of interest in defining clinicopathologic correlates of disease, particularly for monoclonal gammopathy of renal significance.[1–13] Less has been published about MCL which is an aggressive subtype of B-cell non-Hodgkin lymphoma that is characterized by a recurrent genetic translocation, t(11;14), involving the gene encoding cyclin D1 in approximately 85% of cases.[14] MCL-

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associated kidney dysfunction has been documented only in case reports, with authors reporting polyclonal IC mediated GN,[15–23] C3GN,[24,25] and pauci-immune crescentic GN,[26] as well as frequent renal infiltration by lymphoma.[17–19,21–24,26,27] In this study, we initiated a multi-institutional retrospective review to describe the clinicopathologic spectrum of MCL-associated kidney injury, treatment, and outcomes.

METHODS

This study was approved by the institutional review boards of The University of British Columbia, University of Washington, Oregon Health & Science University, Stanford University, Cedars Sinai Medical Center, and University of Los Angeles, and adheres to the Declaration of Helsinki. Native kidney pathology databases were searched from 2000 through 2020 for the term "mantle cell lymphoma," identifying 30 patients: 28 patients with kidney biopsies (2 with repeat biopsies) and 2 autopsy cases. MCL was considered active if it was untreated, currently undergoing treatment, or if it had relapsed or was resistant to therapy. MCL was considered treated if the patient had undergone treatment and was reported to be in remission. Additional specifics on hematologic response were not collected. Biopsies had standard pathologic workup, including light microscopic evaluation with Jones methenamine silver, periodic acid–Schiff, hematoxylin and eosin, and trichrome stains. For immunofluorescence (IF) microscopy, frozen tissue was stained with antibodies against IgG, IgA, IgM, C3, C1q, fibrin/fibrinogen, κ light chain, lambda light chain, and albumin. IgG subclass staining was performed in 3 cases (case numbers [#]1, #2, and #8); pronase digestion paraffin IF was performed in 2 (cases #2 and #17). Phospholipase A2 receptor staining was performed in 2 cases (case #8 and #9); tissue testing for additional MN associated antigens was performed in 2 cases (case #8 and #9). Serum evaluation for alternative complement pathway abnormalities was not performed. Characterization of the interstitial inflammatory infiltrate was performed by immunohistochemistry, *in situ* hybridization, and/or fluorescence *in situ* hybridization. Electron microscopy was performed on all available biopsies. Clinical history was obtained through discussion with nephrologists and review of the medical record whenever available. Renal response criteria were adapted from the Kidney Disease: Improving Global Outcomes response criteria for lupus nephritis: reduction in proteinuria to <0.5 g/g and stabilization or improvement in kidney function.[28]

RESULTS

In total, 30 patients with MCL and relevant kidney pathology were identified (30 biopsies from 28 patients, plus 2 autopsies), with a median age of 67 (range 48–87) years, 73% of whom were men (detailed case information provided in Supplementary Material, Table S1). These patients were subsequently categorized into 2 main groups (Figure 1). One group contained patients with active MCL ($n = 20$) and kidney dysfunction; these patients were subdivided into those with renal abnormalities due or potentially due to MCL ($n = 14$) and those of other or uncertain etiologies ($n = 6$). A second group ($n = 10$) was comprised of patients with treated MCL who were in remission at time of biopsy and had biopsy findings either attributable to MCL-related treatments or other causes.

Kidney Biopsies and Outcomes in Patients With IC or C3 Disease Associated With MCL

A total of 20 patients had active MCL at the time of kidney tissue evaluation (19 with biopsies, 1 autopsy), at least 11 of whom (55%) had glomerular and/or extraglomerular IC or C3 disease (Table 1, cases #1–#11). These 11 patients had a median age of 68 (range 59–87) years, were predominantly men (82%), and presented with AKI (64%), proteinuria (82%, nephrotic range in 36%), and/or hematuria (36%). Comorbid conditions included hypertension (54%) and/or diabetes (27%); 4 had positive autoimmune serologies but none had defined autoimmune disease. No patient had hepatitis B or C virus, HIV, SARS-CoV-2, or other chronic viral and/or bacterial infections. Two patients had other solid-organ malignancies which had been previously treated (case #1 and #5). A total of 4 patients had a detectable paraprotein on serum (serum protein electrophoresis [SPEP]) or urine protein electrophoresis. Overall, 6 patients with IC or C3GN had available follow-up and were treated for MCL, all with clinical remission of GN.

Patterns of IC disease were diverse and consisted of PGNMID (2 patients; Figure 2a-c), C3GN (2 patients; Figure 3a-f), secondary MN (3 patients; Figure 4a-d), and/or polyclonal TBM deposits (2 patients; Figure 4b), and modest lupus-like GN (2 patients). Lymphomatous infiltration was present in 8 patients and often diffuse; 5 also had concurrent IC or C3 lesions. Notably, in most patients, the IC lesions were polyclonal with only 2 PGNMID. In one of these (case #1), both the lymphoma and glomerular immune deposits demonstrated κ light chain restriction, although no circulating paraprotein was identified. In the other PGNMID (case #2), there was discordant staining, i.e. a lambda light chain restricted MCL accompanied by a small IgG-λ

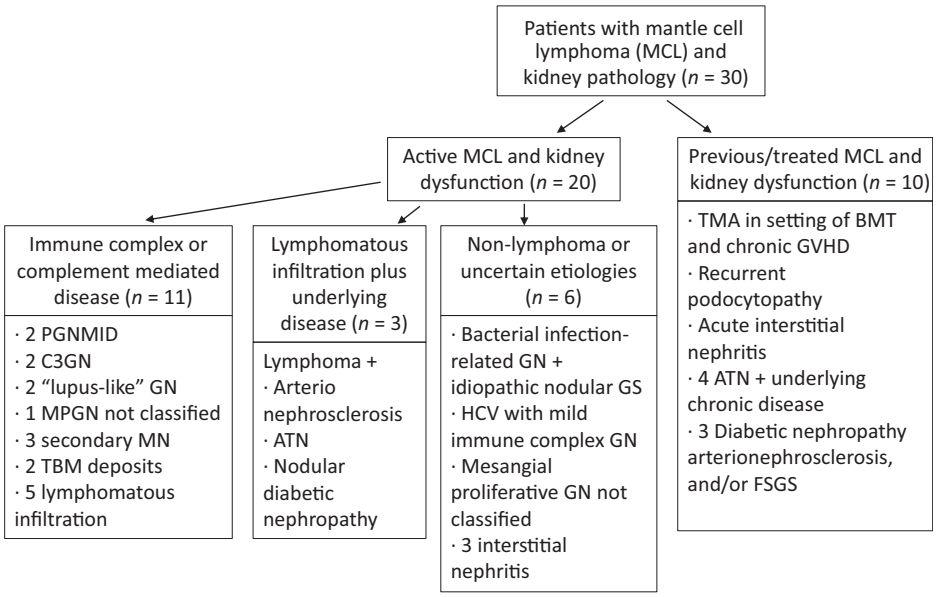

Figure 1. Study schema, patients with kidney pathology and mantle cell lymphoma. ATN, acute tubular necrosis; BMT, bone marrow transplant; FSGS, focal segmental glomerulosclerosis; GN, glomerulonephritis; GS, glomerulosclerosis; GVHD, graft versus host disease; HCV, hepatitis C virus; MCL, mantle cell lymphoma; MN, membranous nephropathy; PGNMID, proliferative glomerulonephritis with monotypic Ig deposits; TBM, tubular basement membrane.

paraprotein spike on SPEP and urine protein electrophoresis, but glomerular ICs which stained for IgG3 κ. For patient #1, MCL was treated with rituximab, bendamustine, and prednisone with subsequent remission of both the MCL and GN (serum creatinine [Cr] 1.4 mg/dl from 4.6 mg/dl, and proteinuria 0.17 g/g from >10 g/g at presentation), maintained after 7 months of follow-up. For patient #2, treatment of MCL with rituximab and bendamustine resulted in remission of GN at 3 months (Cr 2.1 mg/dl from 4.8 mg/dl, and proteinuria 0.9 g/g from 9 g/g), but he died 5 months after kidney biopsy.

The 2 cases of C3 dominant GN met published criteria for C3GN (IF staining for C3 which was ≥2+ greater than any other immune reactant).[29,30] One patient (case #3A) without an identified paraprotein had C3-only deposits in a mesangial and rare subepithelial distribution and mild diabetic glomerulopathy. Although the findings were initially favored to represent postinfectious GN, the changes persisted on repeat biopsy 6 months later (case #3B) and no source of infection was ever identified. The second (case #4) had a history of pneumonia 3 months before kidney biopsy, and an IgM-λ paraprotein on SPEP which was discrepant from the κ light chain restriction of the MCL. Patient #3 began treatment for MCL after the second kidney biopsy, and after 6 years of follow-up, both MCL and GN had resolved (Cr 1.5 from 7.4 mg/dl at presentation). Patient #4 was treated for MCL with rituximab and bendamustine with rapid resolution of the GN; at 28 months of follow-up, both MCL and GN remained in remission (Cr 1.2 mg/dl from 3.2 mg/dl, no hematuria or proteinuria, from 3.2 g/g at diagnosis).

A total of 3 patients had polyclonal or unclassified IC disease. This included 2 (case #5 and #6) mesangial proliferative GNs with moderate staining for polyclonal IgG, C3, and C1q; one of which was in a patient with new positive antinuclear antibody and antidouble stranded DNA and lymphomatous kidney infiltration, but had neither systemic symptoms nor preceding diagnosis of lupus. One patient (case #7) had a membranoproliferative GN and lymphomatous infiltration but no frozen tissue for IF characterization of deposits and preceded use of pronase-digested paraffin IF.

Two of 3 patients with secondary MN (cases #8, #9, and #10) presented with nephrotic syndrome. Two (case #9 and #10) had a positive antinuclear antibody, one of whom also had positive p- anti-neutrophil cytoplasmic autoantibody, antidouble stranded DNA, antiribonucleoprotein, Sjogren Syndrome A, and urine protein electrophoresis (case #10); none had non-MCL malignancies. Immune deposits were composed of polyclonal IgG in a segmental subepithelial (1), mesangial (1), and subendothelial (2) distribution. Both tested cases were negative for phospholipase A2 receptor; one was also negative for neural epidermal growth factor-like 1, and the other was positive for thrombospondin type 1 domain containing 7A (case #8). Follow-up was available in 2 patients (case #9 and #10), both of whom were treated with rituximab and subsequent

Table 1. Patients with active mantle cell lymphoma and renal biopsy finding attributable to MCL (14 patients, 11 with immune complex or complement-mediated disease)

Case	Age sex	Bx indication	Summary of laboratories	Kidney Bx diagnosis	Light microscopy	IF	EM deposit location	Follow-up
1	66 F	AKI, nephrotic proteinuria, hematuria	Low C4, cryo neg, paraprotein neg	PGNMID	MPGN with diffuse crescents	IgG3 κ (2+), C3 (3+), C1q (2-3+)	Mes, subendo	MCL treated, GN in remission at 7 months
2	65M	AKI, nephrotic syndrome, hematuria	Paraprotein pos (λ), discordant from glomerular deposits	PGNMID	Mesangial, endocapillary proliferative, focal crescents	IgG3 κ (3+), C3 (3+), C1q (2-3+)	Mes, subendo, rare subepi	MCL treated, GN in remission at 3 months
3A	68M	AKI, proteinuria, hematuria	Serologies and paraprotein neg	C3 dominant GN	Mesangial proliferative	C3 (3+)	Mes, rare subepi	Persisted on repeat bx at 6 months, then MCL treated and GN in remission at 6 years
3B		Edema, decreased urine output		C3GN	Mesangial proliferative	C3 (3+), C1q (tr-1+)	Mes, rare subepi	
4	61M	AKI, subnephrotic proteinuria, hematuria	Paraprotein pos (λ), discordant from lymphoma (κ)	C3GN, Lymphoma infiltration	Mesangial proliferative	C3 (4+), IgG (2+), k (2+), l (2+), C1q (1-2+)	Mes	MCL treated, GN in remission at 28 months
5	87M	AKI, subnephrotic proteinuria, hematuria	Serologies and paraprotein neg	Modest lupus-like GN, AIN	Mesangial proliferative, mild AIN	C3 (2-3+), C1q (2+), IgG (tr-1+), k (tr-1+), l (tr-1+)	Mes, parames	Unknown
6	76M	AKI	ANA, dsDNA pos, no systemic lupus symptoms	Modest lupus-like GN, Lymphoma infiltration	Mesangial proliferative, duplicated GBM	IgG, IgM, k, l, C3, C1q (all 1+)	Mes, subendo, rare TRI	Unknown
7	73M	Progressive CKD subnephrotic proteinuria	RF pos, paraprotein neg	MPGN, Lymphoma infiltration	MPGN	No glomeruli available	Mes, subendo, few subepi	Unknown
8	66M	Nephrotic syndrome	Serologies and paraprotein neg	MN, PLA2R-, THSD7A+	membranous	IgG (4+), k (2+), l (3+), C3 (3+)	Global subepi, rare mes	Unknown
9	59 F	Nephrotic syndrome	ANA pos, C3 low	MN, PLA2R-, NELL1-Lymphoma infiltration	membranous	IgG (3+), k (2+), l (3+), C3 (3+), with TBM deposits	Irregularly distributed subepi, TBM	MCL treated, GN in remission at 5 years
10	69M	Progressive CKD, subnephrotic proteinuria	ANA, dsDNA, pANCA, RNP, SSA, and paraprotein pos	MN, segmental, with TBM deposits Lymphoma infiltration	membranous	IgG (2+), k, l, C3, C1q (all 1-2+), with chunky TBM deposits	Subepi, subendo, mes, TBM	MCL treated, GN in remission at 17 months
11	77M	AKI	Paraprotein pos	TBM deposits, ATI	ATI, normal glomeruli	Coarse TBM staining for IgG, k, l, C3	Fine granular TBM	Unknown
12	72 F	AKI	Hx Sjogren's, ANA, paraprotein+	Lymphoma infiltration, arterionephrosclerosis	Normal glomeruli	Negative	Negative	Unknown
13	67 F	AKI	Unknown	Lymphoma infiltration, ATI	ATI, normal glomeruli	Negative	Negative	Unknown
14	74M	AKI (autopsy)	Blood cultures pos	Lymphoma infiltration, diabetic nephropathy	Nodular mesangial sclerosis	Not performed	Not performed	(Autopsy)

AIN, acute interstitial nephritis; AKI, acute kidney injury; ANA, antinuclear antibody; ATI, acute tubular injury; Bx, biopsy; CKD, chronic kidney disease; Cryo, cryoglobulin; dsDNA, double stranded DNA; EM, electron microscopy; F, female; GBM, glomerular basement membrane; GN, glomerulonephritis; Hx, history; IF, immunofluorescence; M, male; MCL, mantle cell lymphoma; Mes, mesangial; MN, membranous nephropathy; MPGN, membranoproliferative glomerulonephritis; Neg, negative; NELL1, neural epidermal growth factor-like 1; pANCA, p-antineutrophil cytoplasmic autoantibody; PGNMID, proliferative glomerulonephritis with monoclonal Ig deposits; PLA2R, phospholipase A2 receptor; Pos, positive; RF, rheumatoid factor; RNP, ribonucleoprotein; SSA, Sjogren syndrome A; Subendo, subendothelial; Subepi, subepithelial; TBM: tubular basement membrane; THSD7A, thrombospondin type 1 domain containing 7A; TRI, tubuloreticular inclusions.

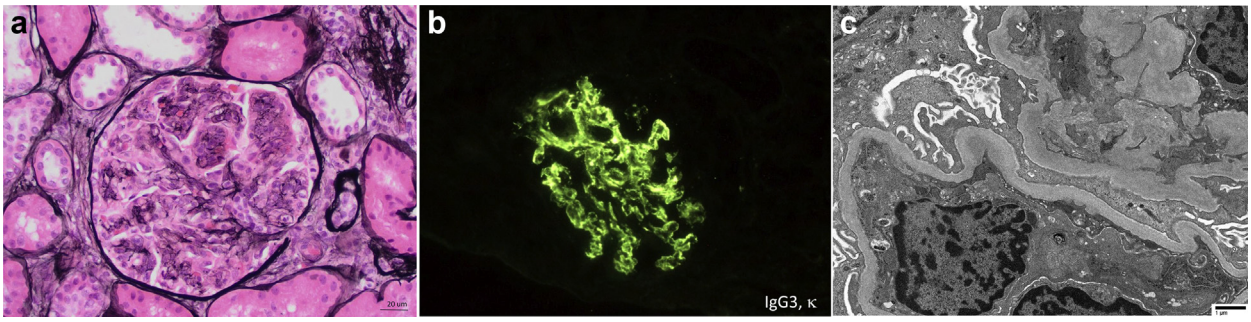

Figure 2. PGNMID (case #1), with (a) proliferative glomerulonephritis (Jones ×200), (b) granular mesangial and peripheral capillary wall immune deposits which stain for IgG3 and κ light chain by immunofluorescence, and (c) mesangial and subendothelial immune deposits without substructural organization by electron microscopy (direct magnification ×2900). PGNMID, proliferative glomerulonephritis with monotypic Ig deposits.

bone marrow transplant, with clinical resolution of GN (case #9: Cr stable at 1.1 mg/dl with no proteinuria at 5 years, and case #10: Cr 1.64 mg/dl from 3.2 mg/dl, proteinuria 0.26 g/g from 2.5 g/g at 17 months).

Diffuse granular TBM immune deposits composed of polyclonal IgG were present in 2 (case #10 and #11), one of which also had segmental MN (case #10). A definitive etiology for the TBM immune deposits was not identified in either case; patients had normal complement levels, no established autoimmune disease or infection, and biopsies lacked other features of IgG4-related disease. Testing for anti-low density lipoprotein receptor related protein 2 (megalin)/anti-brush border antibody disease was not performed, and this possibility cannot be excluded.

In addition to 11 patients with IC or C3 disease associated with MCL, 3 of 20 patients with active MCL had renal dysfunction considered likely related to lymphomatous infiltration of the kidney and/or underlying disease (Table 1, case #12–#14). These 3 patients presented with AKI; 1 had pre-existing Sjogren syndrome and a positive SPEP, and 1 had diabetes, hypertension, and sepsis from endocarditis (autopsy). Kidney histology revealed infiltration by MCL, with the additional finding of arterionephrosclerosis (case #12), acute tubular injury (case #13), and diabetic nodular mesangial sclerosis (case #14).

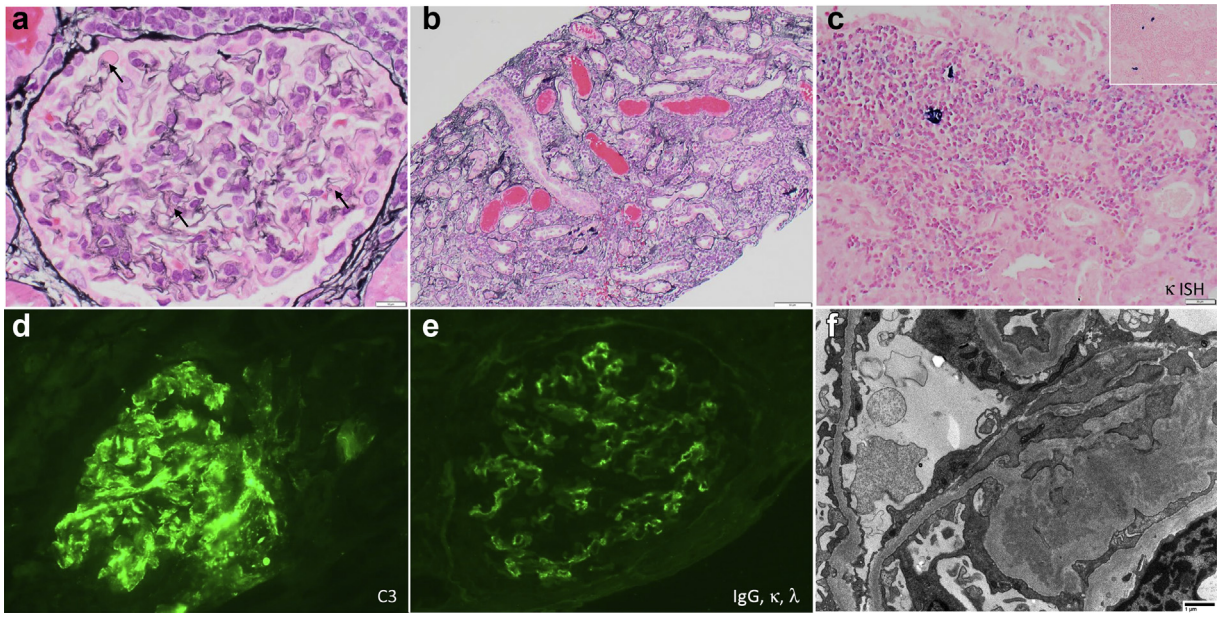

Figure 3. C3GN (case #4), with (a) subtle eosinophilic, predominantly mesangial immune deposits (arrows, Jones ×400), (b) tubulointerstitial lymphomatous infiltration (Jones ×100) composed of (c) κ restricted B-cells with t(11;14) and immunophenotypic features characteristic of mantle cell lymphoma (×200, κ ISH, with negative λ ISH in upper right inset). (d) Glomeruli had granular mesangial and segmental peripheral capillary wall staining for C3, with (e) a lesser degree of predominantly mesangial staining for polyclonal IgG and C1q and (f) mesangial immune deposits (direct magnification ×2900). GN, glomerulonephritis; ISH, *in situ* hybridization.

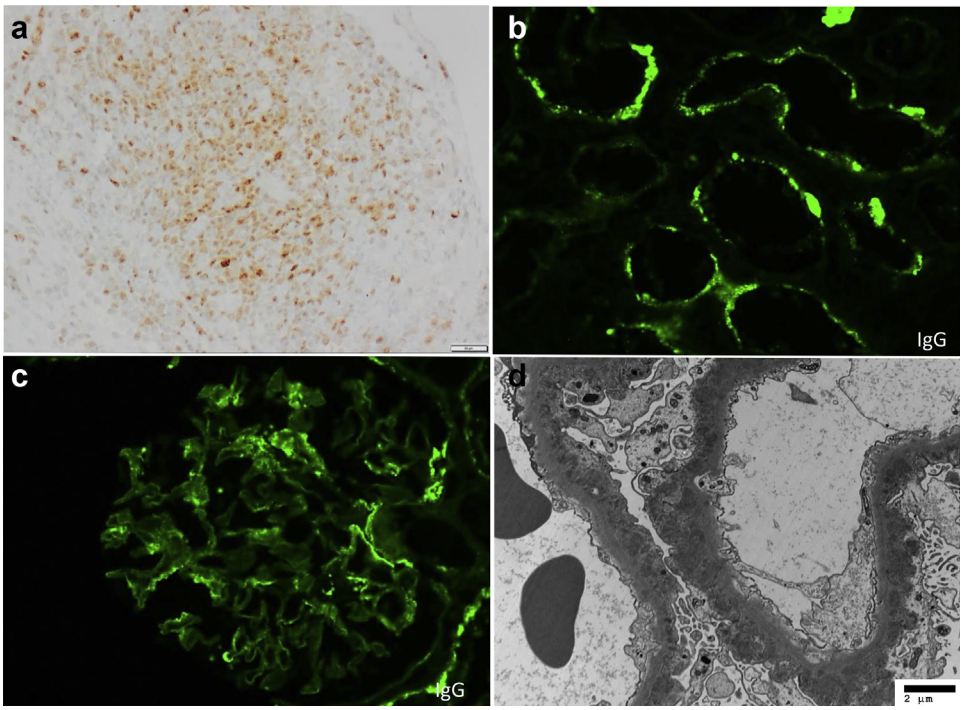

Figure 4. Diffuse parenchymal infiltration by (a) cyclin D1-positive mantle cell lymphoma by immunohistochemistry (×200), (b) granular to chunky tubular basement membrane immune deposits composed of polyclonal IgG and complement, with (c) segmental peripheral capillary wall, mesangial, and Bowman's capsule staining for polyclonal IgG and complement by immunofluorescence and (d) corresponding predominantly subepithelial immune deposits by electron microscopy (direct magnification ×4800).

Kidney Biopsies and Outcomes in Patients With Active MCL and Kidney Dysfunction of Uncertain or Nonlymphoma Etiologies

A total of 6 of 20 patients (30%) with active MCL and kidney dysfunction had biopsy findings of uncertain or nonlymphoma etiologies (Figure 1 and Table 2). All had AKI; proteinuria (67%) and hematuria (83%) were common, but none had a circulating paraprotein or autoimmune disease. Two patients had glomerular IC disease; 1 (case #15) had a history of long-term smoking and a leg ulcer treated with antibiotics, and biopsy demonstrated features of bacterial infection related GN superimposed on idiopathic nodular glomerulosclerosis; another (case #16) had a modest IC GN favored due to hepatitis C virus. Both patients had active untreated MCL, and potential contribution of

Table 2. Patients with active MCL at time of renal biopsy, kidney biopsy findings of uncertain etiology or favored due to other diseases (6 patients)

Case	Age sex	MCL status	Other history	Bx indication	Kidney Bx diagnosis	Follow-up
15	63M	Active, untreated	Long-term smoking, leg ulcer. No DM	AKI, proteinuria	Favor infection related GN, and idiopathic nodular glomerulosclerosis	Treatment and kidney outcome not available. Active lymphoma 4 yr after bx
16	57M	Active, untreated	HCV infection	AKI, subnephrotic proteinuria, hematuria	Modest immune complex GN (IgM, C3 with focal crescent and FSGS) favor related to HCV, mild AIN	Treated with steroids, no improvement in renal function
17	65M	Active, on rituximab	Neutropenic fever. No DM, smoking, or HTN	AKI, subnephrotic proteinuria	Mesangial proliferative glomerulopathy of uncertain etiology, no immune deposits	MCL treated, glomerulopathy in remission at 2.5 yr
18	80F	Active, on rituximab, bendamustine	Allopurinol, IV contrast	AKI, subnephrotic proteinuria rash	AIN with eosinophils	MCL treated, death within 1 yr of biopsy
19	82M	Active, on rituximab, bendamustine	Unknown	AKI, eosinophilia	Mild AIN	MCL treated, outcome not available
20	65M	Preceded by 2 yr, on rituximab and bendamustine	HTN	AKI, hematuria	Mild chronic interstitial nephritis	MCL treated, normal renal function at 5.5 yr

AIN, acute interstitial nephritis; AKI, acute kidney injury; Bx, biopsy; DM, diabetes mellitus; F, female; FSGS, focal segmental glomerulosclerosis; GN, glomerulonephritis; HCV, hepatitis C virus; HTN, hypertension; M, male; MCL, mantle cell lymphoma.

Table 3. Previously reported cases of patients with MCL and kidney biopsies

Age, sex	MCL status	Biopsy indication	Laboratory evaluation	Kidney biopsy	Intervention	Follow-up	Reference
Polyclonal immune complex disease							
68M	MCL diagnosed 5 months later	AKI (Cr 11.8 mg/dl)	ANA, ANCA, anti-GBM, cryoglobulin, SPEP, C3 and C4, ASO, negative/ normal	Proliferative GN with IgG, C3	MCL treated with chlorambucin and prednisolone	Improved: Cr 2.49 mg/dl at 8 mo. Lymphoma responded	31
68M	Active, untreated	AKI (Cr 4.8 mg/dl), 4+ proteinuria	Low C3. ANA, ANCA, HIV, hepatitis, C4 normal	MPGN with polyclonal IgG, IgM	MCL treated with rituximab and hyper CVAD	Improved: Cr 0.5 mg/dl, 1+ proteinuria at 3 mo	16
65M	Active, untreated	Nephrotic syndrome, 6.9 g proteinuria/day and AKI (1.85 mg/dl)	Negative serologies, SPEP, and cryoglobulin	MPGN with IgG, C3, C1q. Lymphoma infiltration	MCL treated with CHOP	Improved: alive at 1 yr (Cr 1.1 mg/dl)	17
54M	Active, untreated	AKI (Cr 6.9 mg/dl), 2.1 g proteinuria on 24 h	Low C3. ANA, ANCA, anti-GBM, HIV, hepatitis, C4 normal	Proliferative GN with crescents, with IgG (2+) and C3 (2+). Lymphoma infiltration	MCL treated with CHOP	Improved urine output and Cr (<3 mg/dl) at 8 wk	18
77M	Active, untreated	AKI (Cr 3.56 mg/dl), anasarca with 14.9 g proteinuria on 24-h	Low C3, C4, positive RF, SPEP: monoclonal IgG-λ and IgM-κ. Positive cryoglobulin. Negative hepatitis serologies	MPGN, with IgG (1+), IgM (1-2+), C3 (1-2+), C1q (1+), k (1-2+), l (tr) Lymphoma infiltration	MCL treated with rituximab, prednisone	Improved renal function at 2 wk (Cr 2.5 mg/dl, 8.9 g/g uPCr), but died of disease at 3 mo	19
58M	Active, untreated	AKI (Cr 3.18 mg/dl), hematuria	ANA, ANCA, C3, C4, HCV, HBV, HIV, SPEP negative/ normal	Proliferative immune complex mediated GN, with C3 (4+), IgG (3+), IgM (2+)	MCL treated with R-CHOP	Normal renal function: Cr 1.2 mg/dl at 3 mo	20
74M	Relapsed MCL, initial diagnosis and treatment 15 years earlier	Nephrotic syndrome with 8.4 g/g uPCr, and AKI (Cr 2.4 mg/dl)	SPEP and UPEP: IgM-lambda. ANA, dsDNA positive	Proliferative GN with crescents, with glomerular IgG, IgM, C3, C1q, thought to represent de novo lupus nephritis. Lymphoma infiltration	MCL treated with rituximab, bortezomib	Improved: Cr 2 mg/dl and proteinuria 3.8 g/g at 3 mo	21
58M	Active, untreated	AKI, 3.8 g/g proteinuria	ANA, ANCA, C3, C4, HIV, hepatitis serologies negative	MPGN with IgG (3+), IgM (2+), C3 (3+), and C1q (3+) with crescents. Lymphoma infiltration	MCL treated with chemotherapy and rituximab	Normal renal function at 6 mo	22
56M	Active, untreated	AKI, (Cr 6 mg/dl) subnephrotic proteinuria (1.1 g/g)	Positive PR3 ANCA. C3, C4 normal	Proliferative immune complex mediated GN with IgG, IgM, C3, C1q, crescents. Lymphoma infiltration	MCL treated	Normal renal function: Cr 1.02 mg/dl at 4 mo	23
C3 glomerulonephritis							
59M	Active, untreated	AKI (Cr 8.7 mg/dl), nephrotic syndrome with 6.9 g proteinuria on 24 h	Low C3 and C4, and positive dsDNA. Negative ANA, ANCA,	MPGN with crescents, C3 only. Lymphoma infiltration	MCL treated with cyclophosphamide, prednisone	Normal kidney function with minimal proteinuria (0.25g) at 3 wk	24
65M	Active, on treatment	AKI (Cr 12.5 mg/dl) nephrotic proteinuria (4 g/ g)	Deletion of CFHR1 and CFHR3 genes. HIV, hepatitis serologies negative	Crescentic C3GN, without mesangial or endocapillary hypercellularity	Methylprednisolone. MCL treated with R-CHOP	Improved: Cr 2 mg/dl, proteinuria <300 mg/d at 12 mo	25
Pauci-immune complex crescentic GN							
77M	Active, untreated	AKI (Cr 5.3)	Positive PR3, ANCA, low C3 and C3, positive ANA.				26

(Continued on following page)

Table 3. (Continued) Previously reported cases of patients with MCL and kidney biopsies

Age, sex	MCL status	Biopsy indication	Laboratory evaluation	Kidney biopsy	Intervention	Follow-up	Reference
			Negative SPEP, HIV, hepatitis serologies	Pauci-immune complex focally crescentic GN. Lymphoma infiltration	MCL treated with cyclophosphamide, vincristine, prednisone	Regained renal function, came off dialysis, but died at 8 mo	
Renal infiltration only							
69M	Relapsed MCL, initial diagnosis and treatment 3 yr earlier	AKI (Cr 11.1 mg/dl)	ANA, ANCA, anti-GBM, HIV, hepatitis serologies negative. C3, C4 normal	Diffuse parenchymal lymphoma infiltration. No GN	Patient declined further chemotherapy	ESKD, died 12 mo later	27
Proliferative GN, not further described							
52M	Active, untreated	AKI	Hepatitis and ASO serologies negative. Cryoglobulin negative	Proliferative GN	MCL treated with Adriamycin, cyclophosphamide, prednisone	Normal kidney function, and remission of lymphoma	32
75M	MCL diagnosed 23 mo later	AKI (Cr 6.5 mg/dl)	ANA, ANCA, anti-GBM, cryoglobulin, SPEP, C3 and C4 negative/normal	Proliferative GN with crescents	GN treated with cyclophosphamide, prednisone, and azathioprine. MCL later treated with chlorambucil	Minimal initial improvement in kidney function (Cr 4.5 mg/dl); died of disease 10 mo after MCL diagnosis	31

AKI, acute kidney injury; ANA, antinuclear antibody; ANCA, antineutrophil cytoplasmic antibody; ASO, antistreptolysin O; CHOP, cyclophosphamide, doxorubicin, vincristine, prednisone; Cr, creatinine; CVAD, Central venous access device; dsDNA, double stranded DNA; ESKD, end-stage kidney disease; F, female; GBM, glomerular basement membrane antibody; GN, glomerulonephritis; HBV, hepatitis B virus; HCV, hepatitis C virus; M, male; MCL, mantle cell lymphoma; MPGN, membranoproliferative glomerulonephritis; R-CHOP, rituximab, cyclophosphamide, doxorubicin, vincristine, prednisone; RF, rheumatoid factor; SPEP, serum protein electrophoresis; uPCr, urine protein-to-creatinine ratio; UPEP, urine protein electrophoresis.

lymphoma to the GN is uncertain. One patient (case #17) had a recent diagnosis of MCL undergoing rituximab treatment, with neutropenic fever, hypocomplementemia, AKI, and subnephrotic proteinuria but no identifiable infection. Kidney biopsy demonstrated an unusual mesangial proliferative glomerulopathy without detectable ICs by routine or paraffin IF or electron microscopy. No other cause was identified for the glomerulopathy (no history of diabetes, smoking, or hypertension), and at 2.5 years of follow-up, MCL was in remission and renal function and proteinuria had improved (Cr 1.4 mg/dl from 2.8 mg/dl, with minimal proteinuria). The etiology of this mesangial proliferative glomerulopathy and its relationship to MCL are uncertain; it is possible that concurrent rituximab treatment in this patient altered biopsy findings. A total of 3 patients had interstitial nephritis (case #18–#20); one of them presented with a rash consistent with lymphoma cutis and had recently received i.v. contrast (case #18). Potential nephrotoxic agents were not identified in the other 2 cases. All were receiving rituximab and bendamustine for MCL, neither of which are generally associated with hypersensitivity interstitial nephritis.

Kidney Biopsies in Patients With MCL in Remission and Kidney Dysfunction

A total of 10 patients had significant kidney pathology while MCL was in remission; these findings were attributed to various underlying diseases (Figure 1 and Supplementary Material, Table S1). All of these patients had been treated with chemotherapy, and 3 received stem cell transplant. One biopsy demonstrated thrombotic microangiopathy in the setting of bone marrow transplant and chronic graft versus host disease. The other 9 had kidney dysfunction with no likely causal relationship to MCL.

DISCUSSION

In this study, we present the spectrum of renal biopsy findings in the largest cohort of patients with MCL to date. Our findings indicate that in patients with active MCL and kidney dysfunction who underwent renal biopsy, 70% had findings that were due or potentially due to lymphoma. Diverse patterns of polyclonal or monoclonal IC disease or C3GN were seen in 55%; 40% had renal parenchymal lymphomatous infiltration. IC and C3GN in the setting of active MCL were responsive to lymphoma-directed therapy.

The overall findings of this clinicopathologic cohort are well-supported by previous case reports of patients with MCL and kidney biopsies (summarized in Table 3). Of 15 previously reported cases of MCL-associated kidney injury, 9 had a polyclonal IC

mediated GN,[15–23] usually with deposition of IgG, IgM, C3, and C1q. Two had C3GN,[24,25] 1 had a pauci-IC crescentic GN,[26] 9 had direct parenchymal infiltration by MCL,[17–19,21–24,26,27] and 2 had a proliferative GN without further available description of IC findings.[31,32] These case reports span 20 years and include a variety of lymphoma treatment approaches. Although establishing causality is difficult, in all of these previously reported cases, kidney dysfunction improved or normalized with treatment of lymphoma. Although our cohort is limited by having clinical follow-up in only 6 of 11 patients with IC or C3GN (2 with PGNMID, 2 with C3GN, and 2 with secondary MN) improvement of kidney disease with lymphoma-directed therapy is consistent with previous studies. We also describe monoclonal IC disease (PGNMID), secondary MN, and TBM immune deposits, which to our knowledge, have not previously been reported in association with MCL.

In some cases, the diversity of IC disease pattern and serologic findings raised the possibility of an unrelated autoimmune disease. Specifically, 4 patients with polyclonal IC disease had either positive autoimmune serologies (including both antinuclear antibody and antidouble stranded DNA in case #6 and #10; antinuclear antibody in case #9) or a modest lupus-like GN (with negative serologies, case #5). However, these patients had no preceding diagnosis of autoimmune disease nor systemic symptoms. There has been a previous report of similar serologic and biopsy findings in a patient with "lupus-like" GN associated with MCL,[21] highlighting this diagnostic pitfall. When considering a GN which does not fit the apparent clinical scenario, occult infection or neoplasia including lymphoproliferative disease are important considerations.

A great variety of paraneoplastic autoimmune and rheumatologic features are well-documented in patients with lymphoma including MCL as well as solid-organ malignancies.[33–36] Paraneoplastic kidney diseases associated with lymphoproliferative disorders but without direct Ig deposition are also well-recognized, and include C3GN,[1,37–40] minimal change disease,[41] thrombotic microangiopathy,[1,42] and pauci-immune vasculitis.[43] Kidney involvement by paraneoplastic Ig deposition most commonly manifests as MN associated with solid-organ malignancies[44,45] and infrequently, other conditions.[44,46,47] Taken together, the cases in our series and review of literature demonstrate that, in comparison to other B-cell lymphomas or plasma cell neoplasms, MCL-associated kidney injury commonly contains C3 or polyclonal immune deposits, suggesting these are driven by systemic immune or complement dysregulation rather than direct deposition of a circulating paraprotein. Mechanisms driving MCL-associated IC disease and underlying immune phenomenon warrant further investigation.

C3GN in the setting of a paraprotein or with masked monoclonal immune deposits is recognized as an monoclonal gammopathy of renal significance-associated lesion.[1,37–40,48] One of our C3GN patients had a circulating paraprotein, but the MCL had discrepant light chain restriction, thereby obscuring the relationship between the lymphoma, paraprotein, and GN. Paraffin IF was not performed in either C3GN cases in our cohort which may have informed more precise classification. Although MCL is generally considered nonsecretory, 2 previous cases of C3GN which responded to MCL-directed therapy have been reported,[24,25] supporting our observations. Thus, C3GN in our MCL cohort was not consistently associated with a paraprotein but nonetheless benefited from treatment of the MCL.

A total of 3 cases had low serum complement levels (case #1 and #17) or a positive rheumatoid factor (case #7) raising the possibility of cryoglobulinemic GN. The biopsies lacked immune thrombi, immune deposit substructure, or even identifiable deposits in a patient with MCL undergoing treatment (case #17). No rash or other systemic symptoms were described, and serum cryoglobulin testing was either not available or negative. It is possible but unlikely that some of these represent cryoglobulinemic GN which we could neither prove nor entirely exclude based on available information.

A total of 5 of 20 patients with active MCL had an identifiable paraprotein on SPEP and/or urine protein electrophoresis, all of whom had kidney dysfunction potentially attributable to lymphoma. However, none of these cases had monoclonal glomerular deposits which matched the circulating protein. Notably, case #2 had PGNMID with κ-restricted deposits but λ paraproteinemia and lambda-restricted lymphoma. We are unable to explain this discordance, but we and others[49] have observed rare cases of PGNMID with glomerular deposits discordant from the light chain restriction of the paraproteinemia or lymphoproliferative disorder. Given the low rate of detection of paraproteinemia in PGNMID in general (20%–30%),[50,51] this apparent discrepancy may be related to undetected clonal or paraneoplastic oligoclonal processes, which may be better detected by new and more sensitive methods[52,53] which were not available for routine clinical practice. The relative infrequency of monoclonal deposits in MCL is distinct from IC disease found in plasma cell neoplasia and low grade B-cell lymphomas, which often but not always have injury related to direct kidney deposition or filtration of the monoclonal protein, such as in PGNMID, monoclonal Ig

deposition disease, cryoglobulinemic GN, immunotactoid GN, AL amyloid, light chain cast nephropathy, light chain proximal tubulopathy, and others.[1–13]

Weaknesses in this study are those inherent to retrospective case review spanning a long period of time, namely: complete clinical, laboratory, and outcome data were not available for all patients. Tissue for further antigen testing in MN cases was not obtainable and biopsies with TBM deposits were not tested for antilow density lipoprotein receptor related protein 2; the possibility that these represent antibrush border antibody disease cannot be excluded. MCL treatment regimens varied somewhat over time and by institution, but a large portion of patients were treated with a combination of bendamustine and rituximab with good lymphoma and renal response; this is the common treatment in MCL, and is well-tolerated with high response rates.[54] Although MCL treatment is consistently associated with clinical remission of GN in our series and in previous reports regardless of treatment type (Table 3), we did not collect specific laboratory evidence of hematologic response. Correlation with both renal response and hematologic parameters are important touchstones in determining whether IC or C3GN are related to an underlying lymphoproliferative disorder. Even so, therapy which can affect both processes independently makes their relationship difficult to determine in this and other reports of GNs associated with lymphoproliferative disorders. Importantly, our findings do not establish a mechanistic link between MCL and glomerular disease, and it is possible that GN clinically improved due to a variety of factors other than lymphoma remission, including rituximab therapy. Despite these weaknesses, our cohort benefits from the experience of multiple institutions and represents the first series of MCL-associated kidney injury. Reassuringly, our systematic review of previously published isolated case reports largely substantiates our findings.

In conclusion, data from our cohort in addition to previous case reports demonstrate that diverse IC patterns of injury define a broad spectrum of MCL-associated kidney injury. The diversity of IC and C3 mediated disease patterns and complex clinical scenarios can present diagnostic dilemmas, and assembly of this cohort may inform future interpretation of biopsies in patients with MCL. Despite their heterogeneity, these lesions may respond well to MCL-directed therapy.

DISCLOSURES

All the authors declared no competing interests.

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SUPPLEMENTARY MATERIAL

Supplementary File (PDF)

Table S1. Findings in patients with mantle cell lymphoma and kidney biopsies.

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