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, 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.

KEYWORDS: glomerulonephritis; kidney biopsy; lymphoma; Mantle cell lymphoma; MGRS; renal pathology
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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 gammapathy 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.
 associations 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, K 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 K 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
paraprotein spike on SPEP and urine protein electrophoresis, but glomerular ICs which stained for IgG3 K. 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). 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 antidualle 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, antidualle stranded DNA, antinucleonucleoprotein, 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)

<table>
<thead>
<tr>
<th>Case</th>
<th>Age</th>
<th>Sex</th>
<th>Bx indication</th>
<th>Summary of laboratories</th>
<th>Kidney Bx diagnosis</th>
<th>Light microscopy</th>
<th>IF</th>
<th>EM deposit location</th>
<th>Follow-up</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>66</td>
<td>F</td>
<td>AKI, nephrotic proteinuria, hematuria</td>
<td>Low C4, cryo neg, paraprotein neg</td>
<td>PGNMID</td>
<td>MPGN with diffuse crescents</td>
<td>IgG3 k (2+), C3 (3+), C1q (2-3+)</td>
<td>Mes, subendo</td>
<td>MCL treated, GN in remission at 7 months</td>
</tr>
<tr>
<td>2</td>
<td>65</td>
<td>M</td>
<td>AKI, nephrotic syndrome, hematuria</td>
<td>Paraprotein pos (λ), dissociant from glomerular deposits</td>
<td>PGNMID</td>
<td>Mesangial, endocapillary proliferative, focal crescents</td>
<td>IgG3 k (3+), C3 (3+), C1q (2-3+)</td>
<td>Mes, subendo, rare subepi</td>
<td>MCL treated, GN in remission at 3 months</td>
</tr>
<tr>
<td>3A</td>
<td>68</td>
<td>M</td>
<td>AKI, proteinuria, hematuria</td>
<td>Serologies and paraprotein neg</td>
<td>C3 dominant GN</td>
<td>Mesangial proliferative</td>
<td>C3 (3+)</td>
<td>Mes, rare subepi</td>
<td>Persisted on repeat bx at 6 months, then MCL treated and GN in remission at 6 years</td>
</tr>
<tr>
<td>3B</td>
<td></td>
<td></td>
<td>Edema, decreased urine output</td>
<td></td>
<td>C3GN</td>
<td>Mesangial proliferative</td>
<td>C3 (3+), C1q (hr-1+)</td>
<td>Mes, rare subepi</td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>61</td>
<td>M</td>
<td>AKI, subnephrotic proteinuria, hematuria</td>
<td>Paraprotein pos (λ), dissociant from lymphoma (κ)</td>
<td>C3QN</td>
<td>Lymphoma infiltration</td>
<td>C3 (4+), IgG (2+), k (2+), l (2+), C1q (1–2+)</td>
<td>Mes</td>
<td>MCL treated, GN in remission at 28 months</td>
</tr>
<tr>
<td>5</td>
<td>87</td>
<td>M</td>
<td>AKI, subnephrotic proteinuria, hematuria</td>
<td>Serologies and paraprotein neg</td>
<td>Modest lupus-like GN, AIN</td>
<td>Mesangial proliferative, mild AIN</td>
<td>C3 (2-3+), C1q (2+), IgG (hr-1+), k (hr-1+), l (hr-1+)</td>
<td>Mes, paraema</td>
<td>Unknown</td>
</tr>
<tr>
<td>6</td>
<td>76</td>
<td>M</td>
<td>AKI</td>
<td>ANA, dsDNA pos, no systemic lupus symptoms</td>
<td>Modest lupus-like GN, Lymphoma infiltration</td>
<td>Mesangial proliferative, duplicated GBM</td>
<td>IgG, IgM, k, l, C3, C1q (all 1+)</td>
<td>Mes, subendo, rare TRI</td>
<td>Unknown</td>
</tr>
<tr>
<td>7</td>
<td>73</td>
<td>M</td>
<td>Progressive CKD subnephrotic proteinuria</td>
<td>RF pos, paraprotein neg</td>
<td>MPGN, Lymphoma infiltration</td>
<td>MPGN</td>
<td>No glomeruli available</td>
<td>Mes, subendo, few subepi</td>
<td>Unknown</td>
</tr>
<tr>
<td>8</td>
<td>66</td>
<td>M</td>
<td>Nephrotic syndrome</td>
<td>Serologies and paraprotein neg</td>
<td>MN, PLA2R-, THSD7A+</td>
<td>Membranous</td>
<td>IgG (4+), k (2+), l (3+), C3 (3+)</td>
<td>Global subepi, rare mes</td>
<td>Unknown</td>
</tr>
<tr>
<td>9</td>
<td>59</td>
<td>F</td>
<td>Nephrotic syndrome</td>
<td>ANA pos, C3 low</td>
<td>MN, PLA2R-, NELL1-Lymphoma infiltration</td>
<td>Membranous</td>
<td>IgG (3+), k (2+), l (3+), C3 (3+), with TBM deposits</td>
<td>Irregularly distributed subepi, TBM</td>
<td>MCL treated, GN in remission at 5 years</td>
</tr>
<tr>
<td>10</td>
<td>69</td>
<td>M</td>
<td>Progressive CKD, subnephrotic proteinuria</td>
<td>ANA, dsDNA, pANCA, RNP, SSA, and paraprotein pos</td>
<td>MN, segmental, with TBM deposits Lymphoma infiltration</td>
<td>Membranous</td>
<td>IgG (2+), k, l, C3, C1q (all 1-2+), with chunky TBM deposits</td>
<td>Subepi, subendo, mes, TBM</td>
<td>MCL treated, GN in remission at 17 months</td>
</tr>
<tr>
<td>11</td>
<td>77</td>
<td>M</td>
<td>AKI</td>
<td>Paraprotein pos</td>
<td>TBM deposits, ATI</td>
<td>ATI, normal glomeruli</td>
<td>Coarse TBM staining for IgG, k, l, C3</td>
<td>Fine granular TBM</td>
<td>Unknown</td>
</tr>
<tr>
<td>12</td>
<td>72</td>
<td>F</td>
<td>AKI</td>
<td>Hx Sjogren’s, ANA, paraprotein pos</td>
<td>Lymphoma infiltration, arterionephrosclerosis</td>
<td>Normal glomeruli</td>
<td>Negative</td>
<td>Negative</td>
<td>Unknown</td>
</tr>
<tr>
<td>13</td>
<td>67</td>
<td>F</td>
<td>AKI</td>
<td>Unknown</td>
<td>Lymphoma infiltration, ATI</td>
<td>ATI, normal glomeruli</td>
<td>Negative</td>
<td>Negative</td>
<td>Unknown</td>
</tr>
<tr>
<td>14</td>
<td>74</td>
<td>M</td>
<td>AKI (autopsy)</td>
<td>Blood cultures pos</td>
<td>Lymphoma infiltration, diabetic nephropathy Nodal mesangial sclerosis</td>
<td>Not performed</td>
<td>Not performed (Autopsy)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

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.
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 Sjögren 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 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.

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

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

<table>
<thead>
<tr>
<th>Age, sex</th>
<th>MCL status</th>
<th>Biopsy indication</th>
<th>Laboratory evaluation</th>
<th>Kidney biopsy</th>
<th>Intervention</th>
<th>Follow-up</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>68M</td>
<td>MCL diagnosed 5 months later</td>
<td>AKI (Cr 11.8 mg/dl)</td>
<td>ANA, ANCA, anti-GBM, cryoglobulin, SPEP, C3 and C4, ASO, negative or normal</td>
<td>Proliferative GN with IgG, C3</td>
<td>MCL treated with chlorambucil and prednisolone</td>
<td>Improved: Cr 2.49 mg/dl at 8 mo. Lymphoma responded</td>
<td>31</td>
</tr>
<tr>
<td>68M</td>
<td>Active, untreated</td>
<td>AKI (Cr 4.8 mg/dl), 4+ proteinuria</td>
<td>Low C3, ANA, ANCA, HIV, hepatitis, C4 normal</td>
<td>MPGN with polyclonal IgG, IgM</td>
<td>MCL treated with rituximab and hyper CVAD</td>
<td>Improved: Cr 0.5 mg/dl, 1+ proteinuria at 3 mo</td>
<td>16</td>
</tr>
<tr>
<td>65M</td>
<td>Active, untreated</td>
<td>Nephrotic syndrome, 6.9 g proteinuria/day and AKI (1.85 mg/dl)</td>
<td>Negative serologies, SPEP, and cryoglobulin</td>
<td>MPGN with IgG, C3, C1q, Lymphoma infiltration</td>
<td>MCL treated with CHOP</td>
<td>Improved: alive at 1 yr (Cr 1.1 mg/dl)</td>
<td>17</td>
</tr>
<tr>
<td>54M</td>
<td>Active, untreated</td>
<td>AKI (Cr 8.9 mg/dl), 2.1 g proteinuria on 24 h</td>
<td>Low C3, ANA, ANCA, anti-GBM, HIV, hepatitis, C4 normal</td>
<td>Proliferative GN with crescents, with IgG (2+) and C3 (2+)</td>
<td>MCL treated with CHOP</td>
<td>Improved urine output and Cr (&lt; 3 mg/dl) at 8 wk</td>
<td>18</td>
</tr>
<tr>
<td>77M</td>
<td>Active, untreated</td>
<td>AKI (Cr 3.56 mg/dl), anasarca with 14.9 g proteinuria on 24-h</td>
<td>Low C3, C4, positive RF, SPEP: monoclonal IgG-λ and IgM-κ. Positive cryoglobulin. Negative hepatitis serologies</td>
<td>MPGN, with IgG (1+), IgM (1-2+), C3 (1-2+), C1q (1+), k (1-2+), l (tr)</td>
<td>Lymphoma infiltration</td>
<td>Improved renal function at 2 wk (Cr 2.5 mg/dl, 8.9 g/l proteinuria), but died of disease at 3 mo</td>
<td>19</td>
</tr>
<tr>
<td>58M</td>
<td>Active, untreated</td>
<td>AKI (Cr 3.18 mg/dl), hematuria</td>
<td>ANA, ANCA, C3, C4, HCV, HBV, HIV, SPEP negative or normal</td>
<td>Proliferative immune complex mediated GN, with C3 (4+), IgG (3+), IgM (2+)</td>
<td>MCL treated with R-CHOP</td>
<td>Normal renal function: Cr 1.2 mg/dl at 3 mo</td>
<td>20</td>
</tr>
<tr>
<td>74M</td>
<td>Relapsed MCL, initial diagnosis and treatment 15 years earlier</td>
<td>Nephrotic syndrome with 8.4 g/l proteinuria and AKI (Cr 2.4 mg/dl)</td>
<td>SPEP and UPEP: IgM-lambda, ANA, dsDNA positive</td>
<td>Proliferative GN with crescents, with glomerular IgG, IgM, C3, C1q, thought to represent de novo lupus nephritis.</td>
<td>MCL treated with rituximab, bortezomib</td>
<td>Improved: Cr 2 mg/dl and proteinuria 3.8 g/l at 3 mo</td>
<td>21</td>
</tr>
<tr>
<td>58M</td>
<td>Active, untreated</td>
<td>AKI, 3.8 g/l proteinuria</td>
<td>ANA, ANCA, C3, C4, HIV, hepatitis serologies negative</td>
<td>MPGN with IgG (3+), IgM (2+), C3 (3+), and C1q (3+) with crescents.</td>
<td>MCL treated with chemotherapy and rituximab</td>
<td>Normal renal function at 6 mo</td>
<td>22</td>
</tr>
<tr>
<td>56M</td>
<td>Active, untreated</td>
<td>AKI, (Cr 6 mg/dl) subnephrotic proteinuria (1.1 g/l)</td>
<td>Positive PR3 ANCA, C3, C4 normal</td>
<td>Proliferative immune complex mediated GN with IgG, IgM, C3, C1q, crescents.</td>
<td>MCL treated</td>
<td>Normal renal function: Cr 1.02 mg/dl at 4 mo</td>
<td>23</td>
</tr>
<tr>
<td>C3 glomerulonephritis</td>
<td>59M</td>
<td>Active, untreated</td>
<td>AKI (Cr 8.7 mg/dl), nephrotic syndrome with 6.9 g proteinuria on 24 h</td>
<td>Low C3 and C4, and positive dsDNA. Negative ANA, ANCA</td>
<td>MPGN with crescents, C3 only.</td>
<td>Lymphoma infiltration</td>
<td>Normal kidney function with minimal proteinuria (0.25g/l) at 3 wk</td>
</tr>
<tr>
<td>65M</td>
<td>Active, on treatment</td>
<td>AKI (Cr 12.5 mg/dl) nephrotic proteinuria (4 g/l)</td>
<td>Deletion of DHR3 and DHR3 genes. HIV, hepatitis serologies negative</td>
<td>Crescentic C3GN, without mesangial or endocapillary hypercellularity</td>
<td>Methylprednisolone. MCL treated with R-CHOP</td>
<td>Improved: Cr 2 mg/dl, proteinuria &lt;300 mg/dl at 12 mo</td>
<td>25</td>
</tr>
</tbody>
</table>

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

<table>
<thead>
<tr>
<th>Age, sex</th>
<th>MCL status</th>
<th>Biopsy indication</th>
<th>Laboratory evaluation</th>
<th>Kidney biopsy</th>
<th>Intervention</th>
<th>Follow-up</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>Negative SPEP, HIV, hepatitis serologies</td>
<td>Pauci-immune complex locally crescentic GN.</td>
<td>MCL treated with cyclophosphamide, vincristine, prednisone</td>
<td>Regained renal function, came off dialysis, but died at 8 mo</td>
<td></td>
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<tr>
<td>Renal infiltration only</td>
<td></td>
<td></td>
<td></td>
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<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>69M</td>
<td>Relapsed MCL, initial diagnosis and treatment 3 yr earlier</td>
<td>AKI (Cr 11.1 mg/dl)</td>
<td>ANA, ANCA, anti-GBM, HIV, hepatitis serologies negative, C3, C4 normal</td>
<td>Diffuse parenchymal lymphoma infiltration.</td>
<td>No GN</td>
<td>Patient declined further chemotherapy</td>
<td>ESKD, died 12 mo later</td>
</tr>
</tbody>
</table>
| Proli
erative GN, not further described |          |                  |                        |               |              |           |          |
| 52M      | Active, untreated | AKI | Hepatitis and ABO serologies negative, Cryoglobulin negative | Proliferative GN | MCL treated with Adriamycin, cyclophosphamide, prednisone | Normal kidney function, and remission of lymphoma |          |
| 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 |          |

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.

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 due to lymphoma-directed therapy. The overall findings of this clinicopathologic cohort with MCL and kidney biopsies (summarized in Table 3) are well-supported by previous case reports of patients with MCL and related kidney injury. Kidney biopsy associated kidney injury, 9 had a polyclonal IC associated kidney injury, 9 had a polyclonal IC

**DISCUSSION**

Kidney Biopsies in Patients With MCL, Remission and Kidney Dysfunction

A total of 10 patients had significant kidney pathology while MCL was in remission. These findings were attributed to lymphoma-directed therapy. Diverse patterns of polyclonal or monoclonal IC disease or C3GN were seen in 55%, 40% and 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 with MCL and kidney biopsies (summarized in Table S1) are well-supported by previous case reports of patients with MCL and related kidney injury. Kidney biopsy associated kidney injury, 9 had a polyclonal IC 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,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 antidual 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,31 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 malignancies44,45 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 gammapathy 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 cryoglobulinic 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 cryoglobulinic 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 others49 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 methods52,53 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.1,11

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 anti-brush 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.
STROBE Statement (PDF)

REFERENCES
11. Stokes MB, Wood B, Alpers ChE. Membranoproliferative glomerulonephritis associated with low-grade B cell


40. Bridoux F, Desport E, Frémieux-Bacchi V, et al. Glomerulo-


