Rate and Predictors of Finding Monoclonal Gammopathy of Renal Significance (MGRS) Lesions on Kidney Biopsy in Patients with Monoclonal Gammopathy

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ABSTRACT

Background Little is known about the rate and predictors of finding lesions of monoclonal gammopathy (MG) of renal significance (MGRS) on kidney biopsy specimens among patients with MG.

Methods We reviewed the medical records from 2013 to 2018 at the Mayo Clinic in Rochester, Minnesota, to identify patients with MG and whether they had undergone a kidney biopsy. In a more select group of patients with MG from 2017 to 2018, we conducted a review of records to determine how many had underlying CKD, which of those with CKD had undergone a kidney biopsy, and reasons for deferring a kidney biopsy.

Results Between 2013 and 2018, we identified 6300 patients who had MG, 160 (2.5%) of whom had undergone a kidney biopsy. Of the 160 patients, 64 (40%) had an MGRS lesion; amyloid light chain amyloidosis, the most common finding, accounted for nearly half of these lesions. In the non-MGRS group comprising 96 patients, 23 had arteriosclerosis, the most common finding. In multivariate analysis, strong predictors of finding an MGRS lesion included the presence of an elevated free light chain ratio, proteinuria, and hematuria. Among 596 patients with CKD and MG from 2017 to 2018, 62 (10.4%) underwent a kidney biopsy. Kidney biopsy was deferred for 70 patients (20%); for 62 of the 70, the diagnosis was already known, and eight were not candidates for therapy. Younger age and higher proteinuria and serum creatinine levels increased the likelihood that the patient would undergo a kidney biopsy.

Conclusions Proteinuria $\geq 1.5$ g/d, hematuria, and an elevated free light chain ratio increase the likelihood of finding MGRS, and a kidney biopsy should be highly considered in such patients.


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Monoclonal gammopathy (MG) of undetermined significance is defined as the presence of $<3$ g/dl of monoclonal Ig in the serum and $<10\%$ of monoclonal plasma cells on bone marrow (BM) biopsy specimens in the absence of organ damage related to the monoclonal protein.1 Kidney damage secondary to monoclonal protein in the absence of a malignancy such as multiple myeloma (MM), symptomatic Waldenström macroglobulinemia, or symptomatic chronic lymphocytic leukemia (CLL) has been increasingly recognized and is now termed MG of renal significance (MGRS).2 To diagnose MGRS, a renal biopsy is required—except for amyloid light chain amyloidosis (AL-amyloidosis), which can be diagnosed by other means such as
by BM biopsy sample or fat aspirate.3,4 Despite this, great angst remains among the nephrology community as whom to biopsy, especially in the elderly. This is primarily driven by the fact that both MG and CKD are prevalent in the elderly population. In a population-based study from Olmsted County, the rate of MG was 1.7% in patients between the ages of 50 and 60, and it increased to 6.6% in patients >80 years of age.5 Similarly, the prevalence of CKD (defined as eGFR <60 ml/min per 1.73 m² or albumin-creatinine ratio ≥30 mg/g) in patients >60 years is estimated to be >30% and it increases further with age.6 Therefore, it is conceivable that some patients with CKD also have MG, but the monoclonal protein is not the cause of the underlying kidney disease. Currently, little is known regarding clinical predictors of finding an MGRS lesion on a kidney biopsy specimen. In addition, there is limited information in the literature regarding which patients with CKD undergo a kidney biopsy and the exact rate of finding an MGRS lesion as compared with other lesions. Although previous studies have reported on the rate of monoclonal-associated kidney lesions, the studies were either from before 2011 when the term MGRS was introduced, excluded patients with elevated free light chains (FLC), or they included patients with MM or other hematologic conditions that required treatment due to tumor burden and therefore these studies did not report on the true rate of MGRS.7–9

Our first aim was to establish the rate of finding an MGRS lesion in patients with MG who undergo a kidney biopsy and to identify the clinical and laboratory predictors in blood and urine that increase the likelihood of finding such lesions. Our second aim was to identify factors that increased the likelihood that a patient with CKD and MG would be referred to a specialist (nephrologist or hematologist) and would undergo a kidney biopsy.

METHODS

Study Population

This study was conducted at Mayo Clinic (Rochester, MN) and the study was approved by the Institutional Review Board.

For the first aim, we identified all patients that had a positive serum and/or urine monoclonal study within the Mayo Clinic Laboratory System from 2013 to 2018. We subsequently reviewed electronic medical records of patients who received medical care at Mayo Clinic (Rochester, MN) from 2013 to 2018. For completion and homogeneity of monoclonal testing, we included only the patients who were tested for monoclonal studies at Mayo Clinic during the study period. Patients were considered to have MG if they tested positive on any of the following tests: serum protein electrophoresis, serum immunofixation, urine protein electrophoresis, or urine immunofixation. Patients with an abnormal FLC ratio (κ to λ) were also considered to have MG. For patients with eGFR ≥60 ml/min per 1.73 m² a ratio outside the range of 0.27–1.65 was considered abnormal, but for patients with an eGFR <60 ml/min per 1.73 m² any value outside the range of 0.37–3.10 was considered abnormal.10 Patients who had MG in the setting of an underlying hematologic malignancy that required treatment due to tumor burden or symptoms (unrelated to kidney disease) such as MM, Waldenström macroglobulinemia, CLL, or other high-grade lymphomas were excluded. Patients were also excluded if they had ESKD or had a kidney transplant at the time of monoclonal testing or if the monoclonal testing was done ≥12 months after the kidney biopsy sample had been obtained.

After identifying the patients who had MG, we then reviewed the patients’ electronic medical records to identify those who had a kidney biopsy performed. Lesions were considered associated with MGRS based on the consensus guideline by the International Kidney and Monoclonal Gammapathy Research Group.3 Patients with thrombotic microangiopathy were considered to have an MGRS lesion only if no other obvious cause for the thrombotic microangiopathy (such as atypical hemolytic uremic syndrome, thrombotic thrombocytopenic purpura, drugs, underlying autoimmune disease) was identified.11,12

Given that patients with diabetes mellitus (DM) and kidney disease commonly have proteinuria and understanding what factors would increase the likelihood of having an MGRS lesion on a kidney biopsy specimen in this population is important, we also performed a more detailed analysis in this subgroup.

For the second aim, we performed a more comprehensive and detailed review of the medical records of the patients who had MG from 2017 to 2018 to establish how many had underlying CKD and, of those with CKD, which patients underwent a kidney biopsy. We chose a more select group from the recent years because this was more reflective of the current ongoing practices. Patients who did not have a serum creatinine or urinalysis available on their electronic medical record were excluded from this analysis. For the purpose of this study, CKD was defined as having an eGFR <60 ml/min per 1.73 m² based on the CKD–Epidemiology Collaboration equation. Patients with eGFR ≥60 ml/min per 1.73 m² were considered as having CKD if they had evidence of hematuria or proteinuria. Hematuria was defined as having more than three red blood cells per high power field, and proteinuria was defined as

Significance Statement

It is not known how frequently a kidney biopsy specimen reveals monoclonal gammapathy (MG) of renal significance (MGRS) in patients with MG or what factors predict this finding. In a review of medical records of 6300 patients with MG, the authors found that only 160 (2.5%) had a biopsy. Of those, 96 (60%) had lesions unrelated to MG, with arteriosclerosis and diabetic nephropathy accounting for most cases. Among 64 patients with MGRS, amyloid light chain amyloidosis and proliferative GN with monoclonal Ig deposition were the most common lesions. An elevated serum free light chain ratio, proteinuria ≥1.5 g/d, and hematuria were the strongest independent predictors of finding MGRS on biopsy specimens. These findings will assist nephrologists in determining which patients with MG and CKD would be at high risk of having MGRS.
having an estimated 24-hour urinary protein of >300 mg. We further evaluated what factors predicted who was likely to undergo a kidney biopsy. This included a detailed review of the medical records and identifying the underlying comorbidities based on the Charlson Comorbidity Index (CCI). The medical records were also reviewed to assess which patients were seen by a nephrologist and/or a hematologist versus others using two specialists. We identified the reasons as to why a kidney biopsy was not pursued in these patients as well as a detailed analysis of the hematologic workup that was completed (such as BM biopsy or fat aspirate).

**Statistical Analyses**

Data were summarized as mean±SD for continuous variables if normally distributed and median (interquartile range [IQR]) if not normally distributed, and as n (%) for categorical variables. Associations between clinical parameters and urinary and hematologic characteristics with the outcomes of interest (presence of MGRS on kidney biopsy specimen or undergoing a kidney biopsy) were assessed using univariate logistic regressions. Odds ratios (ORs), 95% confidence intervals, and corresponding P values were reported. The multivariate model predicting the odds of outcome of interest was created by the mixed stepwise method. We included age and sex as well as other variables that had a P value in univariate analysis of <0.05. We did not include any variable that had missing values of >10% in the multivariate model. We limited the number of variables in the multivariate model based on the rule of ten events per one predicting variable to avoid over-adjustment. We assessed the performance of the 24-hour urine protein level and evaluated the cutoff level of proteinuria in predicting the presence of MGRS on kidney biopsy specimens by the receiver operating characteristic curve. We also assessed differences in baseline characteristics between AL-amyloidosis MGRS and non-AL-amyloidosis MGRS, in addition to patients with CKD without kidney biopsy who were seen by a nephrologist and/or a hematologist versus others using two-sample unpaired t test. We used JMP Pro version 14.1.0 (SAS institute) for statistical analysis. We considered a P value less than or equal to type I error (α) of 0.05 as statistically significant.

**RESULTS**

**Baseline Characteristics of Patients Who Had a Kidney Biopsy (MGRS versus Non-MGRS)**

We identified a total of 6300 unique patients from 2013 to 2018 who had MG and met the inclusion criteria as noted above (Figure 1). Of the 6300 patients, 160 patients (2.5%) underwent a kidney biopsy. Of the 160 patients who had a kidney biopsy, 64 patients (40%) had an MGRS lesion whereas 96 patients (60%) had a kidney lesion that was unrelated to the monoclonal protein. Overall mean age was 65.9±12.1 years and patients were predominantly male and white. Mean serum creatinine was 2.4±1.7 mg/dl and median proteinuria was 1.65 (IQR, 0.48–4.70) g/dl. DM was present in 23.1% of the cohort.

In the MGRS group, AL-amyloidosis was by far the most common finding (n=5, 43.8%) and accounted for almost half of the MGRS lesions. Proliferative GN with monoclonal Ig deposition (PGNMID) was the second most common lesion (n=12, 18.8%), followed by light chain proximal tubulopathy (LCPT) (n=6, 9.4%), light chain deposition disease (n=5, 7.8%), and type 1 cryoglobulinemic GN (n=5, 7.8%). Other lesions are shown in Figure 1. Of the six patients with LCPT, four patients (66.7%) had evidence of glucosuria in addition to proteinuria (three did not have a diagnosis of DM) and had low uric acid levels (range, 2.2–2.7 mg/dl). None of the patients had hypokalemia or hypophosphatemia.

In the non-MGRS group, arteriosclerosis was the most common finding (n=23, 24.0%), followed by diabetic nephropathy (n=17, 17.7%) and ANCA-associated vasculitis (n=11, 11.5%). Additional lesions are summarized in Figure 1.

**Clinical Predictors of Finding an MGRS Lesion on Kidney Biopsy Specimen**

Patients in the MGRS group had higher proteinuria at the time of kidney biopsy with median proteinuria of 2.75 (IQR, 0.86–6.72) g/dl compared with 1.12 (IQR, 0.29–3.39) g/dl in the non-MGRS group (P=0.001), and were more likely to have hematuria (58.7% versus 35.5%, P=0.004), lower mean C3 levels (87.0±36.6 versus 113±30.2, P=0.003), and were less likely to have DM (12.55% versus 30.1%, P=0.01) (Table 1). Other clinical parameters such as age, sex, race, BP, serum creatinine, or hemoglobin were not associated with increased odds of finding an MGRS lesion.

We also assessed the performance of proteinuria in predicting MGRS on kidney biopsy specimens and we identified the cutoff proteinuria level of 1.5 g/dl to have the highest sensitivity (67.2%) and specificity (58.5%) with an area under the curve of 0.677. Therefore, we chose this cutoff for our analysis.

In the univariate model of the hematologic parameters, having an abnormal FLC ratio increased the odds of finding an MGRS lesion significantly (OR, 6.39; 95% CI. 3.09 to 13.21) and overall the affected to unaffected FLC ratio was significantly higher in the MGRS group compared with the non-MGRS group (OR, 5.64 [95% CI, 2.63 to 21.26]) versus 1.79 [95%CI, 1.06 to 3.5], respectively; P=0.001). Patients with MGRS were more likely to receive a BM biopsy and were more likely to have an abnormal BM biopsy specimen (89.8% in MGRS group versus 60.7% in the non-MGRS group, P=0.003). Patients with MGRS were also more likely to have more plasma cell abnormality on the BM biopsy specimen. In the MGRS group, 65% of patients had ≥5% light chain–restricted plasma cells on the BM biopsy specimen compared with 25% in the non-MGRS group. Other hematologic parameters such as serum or urinary M-spike or the type of heavy chain were not predictive of finding an MGRS lesion (Table 1).
In the multivariate model which took into account age, sex, diagnosis of DM, proteinuria, hematuria, and abnormal FLC, the strongest predictors of finding an MGRS lesion was the presence of an abnormal FLC (OR, 11.04; 95% CI, 4.36 to 27.9) followed by proteinuria $\leq 1.5 \text{ g/d}$ (OR, 3.45; 95% CI, 1.43 to 8.42) and hematuria (OR, 2.94; 95% CI, 1.23 to 7.0) (Table 2).

**Characteristics of Patients with DM Who Underwent a Kidney Biopsy**

Of the 37 patients with a diagnosis of DM and positive monoclonal studies between 2013 and 2018 who underwent a kidney biopsy, 29 (78%) had lesions unrelated to the monoclonal protein with diabetic nephropathy being the most common finding ($n=16$, 55%), followed by IgA nephropathy ($n=3$, 10%), arteriosclerosis ($n=3$, 10%), acute tubular necrosis ($n=2$, 6%), and ANCA-associated vasculitis ($n=2$, 6%). In the MGRS group, the most common lesion was amyloidosis ($n=5$, 62.5%) followed by PGNMID ($n=2$, 25%). The best predictor of finding an MGRS lesion in the diabetic group was the degree of proteinuria (OR, 1.52; 95% CI, 1.06 to 2.17) or the presence of nephrotic-range proteinuria (OR, 6.39; 95% CI, 1.18 to 34.62). The median proteinuria at baseline
in the MGRS group was 5.9 (IQR, 2.1–14.1) g/d versus 1.7 (IQR, 0.4–3.2) g/d in the non-MGRS group. The lowest proteinuria in the MGRS group in a patient with DM was 0.86 g/d. Other clinical parameters were not predictive (Supplemental Table 1).

**Clinical Characteristics of Patients with AL-Amyloidosis versus Nonamyloidosis MGRS**

Patients with amyloidosis were significantly older (68.7±9.1 versus 62.6±13.6, \( P=0.04 \)) and had lower systolic BPs (117±16.9 versus 136±24.1 mm Hg, \( P<0.001 \)) and diastolic BPs (68.0±9.5 versus 77±14.1 mm Hg, \( P=0.007 \)) at baseline compared with the nonamyloidosis MGRS group. Proteinuria was significantly higher in amyloidosis with a median of 4.41 (IQR, 2.00–9.58) g/d compared with 1.65 (IQR, 0.52–6.12) g/d in nonamyloidosis MGRS (\( P=0.022 \)) (Supplemental Table 2). There were no differences in serum creatinine levels or hematuria at time of kidney biopsy between the amyloidosis and nonamyloidosis group. Patients with amyloidosis were

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Overall (n=160)</th>
<th>MGRS Lesions (n=64)</th>
<th>Non-MGRS Lesions (n=96)</th>
<th>OR (95% CI)</th>
<th>( P ) Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (yr)</td>
<td>65.9±12.1</td>
<td>65.3±12.1</td>
<td>66.3±12.2</td>
<td>0.99 (0.97 to 1.02)</td>
<td>0.58</td>
</tr>
<tr>
<td>Male</td>
<td>110 (68.8%)</td>
<td>48 (75.0%)</td>
<td>62 (64.6%)</td>
<td>1.65 (0.81 to 3.32)</td>
<td>0.17</td>
</tr>
<tr>
<td>White</td>
<td>139 (86.9%)</td>
<td>57 (89.1%)</td>
<td>82 (85.4%)</td>
<td>1.39 (0.53 to 3.66)</td>
<td>0.51</td>
</tr>
<tr>
<td>sBP (mm Hg)</td>
<td>127.1±20.5</td>
<td>127.0±23.1</td>
<td>127.1±18.6</td>
<td>1.00 (0.98 to 1.02)</td>
<td>0.97</td>
</tr>
<tr>
<td>dBP (mm Hg)</td>
<td>72.3±11.7</td>
<td>72.7±12.9</td>
<td>72.0±10.9</td>
<td>1.01 (0.98 to 1.03)</td>
<td>0.73</td>
</tr>
<tr>
<td>DM</td>
<td>37 (23.1%)</td>
<td>8 (12.5%)</td>
<td>29 (30.2%)</td>
<td>0.33 (0.14 to 0.78)</td>
<td>0.01</td>
</tr>
<tr>
<td>Serum studies</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Creatinine (mg/dl)</td>
<td>2.4±1.7</td>
<td>2.4±1.8</td>
<td>2.5±1.6</td>
<td>0.95 (0.78 to 1.16)</td>
<td>0.61</td>
</tr>
<tr>
<td>Hemoglobin (g/dl)</td>
<td>11.8±2.4</td>
<td>11.9±2.6</td>
<td>11.7±2.3</td>
<td>1.03 (0.90 to 1.18)</td>
<td>0.69</td>
</tr>
<tr>
<td>C3 level (mg/dl)</td>
<td>104.3±34.5</td>
<td>87.0±36.6</td>
<td>113.0±30.2</td>
<td>0.98 (0.96 to 0.99)</td>
<td>0.003</td>
</tr>
<tr>
<td>C4 level (mg/dl)</td>
<td>26.0±15.1</td>
<td>22.1±17.9</td>
<td>28.0±13.3</td>
<td>0.97 (0.93 to 1.01)</td>
<td>0.12</td>
</tr>
<tr>
<td>Urinary studies</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Urinary protein (g/d)</td>
<td>1.65 (0.48 to 4.70)</td>
<td>2.75 (0.86 to 6.72)</td>
<td>1.12 (0.29 to 3.39)</td>
<td>1.13 (1.04 to 1.23)</td>
<td>0.001</td>
</tr>
<tr>
<td>Proteinuria ≥1.5 g/d</td>
<td>82 (51.9%)</td>
<td>43 (67.2%)</td>
<td>39 (41.5%)</td>
<td>2.89 (1.49 to 5.61)</td>
<td>0.002</td>
</tr>
<tr>
<td>NRP</td>
<td>52 (32.9%)</td>
<td>29 (45.3%)</td>
<td>23 (24.5%)</td>
<td>2.56 (1.29 to 5.05)</td>
<td>0.007</td>
</tr>
<tr>
<td>Hematuria</td>
<td>70 (44.9%)</td>
<td>37 (58.7%)</td>
<td>33 (35.5%)</td>
<td>2.59 (1.34 to 4.99)</td>
<td>0.004</td>
</tr>
<tr>
<td>Dysmorphic RBCs</td>
<td>19 (28.4%)</td>
<td>8 (22.9%)</td>
<td>11 (34.4%)</td>
<td>0.57 (0.19 to 1.67)</td>
<td>0.30</td>
</tr>
<tr>
<td>Hematologic studies</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Clonality</td>
<td></td>
<td></td>
<td></td>
<td>0.68</td>
<td></td>
</tr>
<tr>
<td>Monoclonal</td>
<td>151 (94.4%)</td>
<td>61 (95.3%)</td>
<td>90 (93.8%)</td>
<td>Reference</td>
<td></td>
</tr>
<tr>
<td>Biclonal</td>
<td>9 (5.6%)</td>
<td>3 (4.7%)</td>
<td>6 (6.2%)</td>
<td>0.74 (0.18 to 3.06)</td>
<td></td>
</tr>
<tr>
<td>IgG heavy chain</td>
<td>84 (63.2%)</td>
<td>31 (66.0%)</td>
<td>53 (61.6%)</td>
<td>1.21 (0.57 to 2.54)</td>
<td>0.62</td>
</tr>
<tr>
<td>Serum M-protein (g/dl)</td>
<td>1.1±0.7</td>
<td>1.1±0.8</td>
<td>1.1±0.6</td>
<td>0.96 (0.44 to 2.11)</td>
<td>0.92</td>
</tr>
<tr>
<td>Urine M-protein (g/dl)</td>
<td>0.15 (0.09 to 0.38)</td>
<td>0.16 (0.11 to 0.50)</td>
<td>0.14 (0.07 to 0.28)</td>
<td>3.70 (0.12 to 114.73)</td>
<td>0.42</td>
</tr>
<tr>
<td>( \kappa ) FLC (mg/dl)</td>
<td>4.84 (2.28 to 11.1)</td>
<td>2.90 (1.6 to 11.6)</td>
<td>5.97 (2.99 to 10.93)</td>
<td>1.01 (1.00 to 1.02)</td>
<td>0.19</td>
</tr>
<tr>
<td>( \lambda ) FLC (mg/dl)</td>
<td>3.61 (1.63 to 8.38)</td>
<td>4.12 (1.28 to 13.90)</td>
<td>3.31 (1.90 to 7.13)</td>
<td>1.03 (1.00 to 1.05)</td>
<td>0.05</td>
</tr>
<tr>
<td>Affected/unaffected FLC ratio</td>
<td>2.71 (1.34 to 4.83)</td>
<td>5.64 (2.63 to 21.26)</td>
<td>1.79 (1.06 to 3.50)</td>
<td>1.15 (1.06 to 1.25)</td>
<td>0.001</td>
</tr>
<tr>
<td>Abnormal FLC ratio*</td>
<td>71 (48.3%)</td>
<td>46 (73.0%)</td>
<td>25 (29.8%)</td>
<td>6.39 (3.09 to 13.21)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Received BM biopsy</td>
<td>87 (54.4%)</td>
<td>59 (92.2%)</td>
<td>28 (29.2%)</td>
<td>28.66 (10.40 to 78.95)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Abnormal BM biopsy specimen</td>
<td>70 (80.46%)</td>
<td>53 (89.8%)</td>
<td>17 (60.7%)</td>
<td>5.72 (1.84 to 17.78)</td>
<td>0.003</td>
</tr>
</tbody>
</table>

Values for continuous variables are described as mean±SD or median (IQR) depending on the distribution, and for categoric variables described as count (%). sBP, systolic BP; dBP, diastolic BP; C3, complement 3; C4, complement 4; NRP, nephrotic-range proteinuria; RBCs, red blood cells; LC, light chain.

*Abnormal FLC ratio in patients with eGFR ≥60 ml/min per 1.73 m² is a ratio outside the range of 0.27–1.65 and is a ratio outside the range of 0.37–3.10 in patients with eGFR <60 ml/min per 1.73 m².
Table 2. Multivariable logistic regression analysis of predictors of finding an MGRS lesion on a kidney biopsy specimen in patients with MG

<table>
<thead>
<tr>
<th>Predictors</th>
<th>OR (95% CI)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>0.39 (0.04 to 4.13)</td>
<td>0.43</td>
</tr>
<tr>
<td>Male sex</td>
<td>2.15 (0.84 to 5.56)</td>
<td>0.11</td>
</tr>
<tr>
<td>Proteinuria ≥1.5 g/d</td>
<td>3.45 (1.43 to 8.42)</td>
<td>0.006</td>
</tr>
<tr>
<td>Hematuria</td>
<td>2.94 (1.23 to 7.01)</td>
<td>0.01</td>
</tr>
<tr>
<td>Abnormal FLC ratio</td>
<td>11.04 (4.36 to 27.91)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>DM</td>
<td>0.48 (0.16 to 1.43)</td>
<td>0.18</td>
</tr>
</tbody>
</table>

more likely to have an elevated λ light chain compared with the nonamyloid MGRS group (P<0.001). Additional characteristics are summarized in Supplemental Table 2. Of the 28 patients that had AL-amyloidosis (2013–2018), only three patients had a known diagnosis of AL-amyloidosis before the kidney biopsy was performed. The reason for pursuing a kidney biopsy in these patients despite a known diagnosis of AL-amyloidosis was to rule out other potential causes of CKD due to rapid deterioration of the kidney function. In another four patients, hematologic workup was completed before pursuing a kidney biopsy, but the workup was negative and therefore a kidney biopsy was pursued (Supplemental Figure 1).

Referral Patterns to a Specialist and Reasons for Deferring Kidney Biopsy in Patients with CKD and MG (2017–2018)

Because this was a retrospective study and the decision regarding whether to refer a patient with CKD and MG to a specialist (nephrologist/hematologist) and whether to pursue a kidney biopsy was at the discretion of the treating physician and the data were therefore inherently biased, we evaluated a more select group of patients from 2017 to 2018 more closely to decide how many patients with MG had underlying CKD and, of those patients, how many patients had a kidney biopsy performed. In patients with CKD and MG who did not undergo a kidney biopsy, we looked to see which patients were referred to see a nephrologist and/or a hematologist. In total, we identified 1826 patients with MG from 2017 to 2018. We then excluded the patients that did not have enough information to establish whether they had underlying CKD and identified 1608 patients (Figure 2). Of those, 596 patients (37.1%) had evidence of CKD whereas the majority did not. Of the 596 patients, 62 patients (10.4%) underwent a kidney biopsy and 534 patients (89.6%) did not. These 62 patients are part of the larger cohort of 160 patients who underwent a kidney biopsy between 2013 and 2018 and their results are shown in Figure 1. Of the 534 patients who did not undergo a kidney biopsy, 90 patients were seen only by a nephrologist, 192 were seen only by a hematologist, 72 patients were seen by both, and 180 were seen by neither (Supplemental Figure 2).

Of the 354 patients that were seen by either a hematologist and/or a nephrologist, we looked to see why a kidney biopsy was deferred or why the patient was not referred to see a nephrologist (if seen by a hematologist only). Of the 354 patients, the hematologist was not aware or did not acknowledge that the patient had CKD (n=106), or the nephrologist was not aware or did not acknowledge that the patient had a MG (n=36). Together they accounted for 40% of the cases. In 132 patients (37%), there was a “low suspicion” for MGRS. The reasons for low suspicion were not always provided in the records but “stable kidney function,” “low-grade proteinuria,” or “another potential cause for CKD more likely” were commonly cited. In 62 patients (18%), kidney biopsy was not pursued because it would not have changed the management of the patient. The majority (n=61) of these patients had known AL-amyloidosis and one patient had smoldering myeloma that the hematologist decided to treat regardless of the kidney biopsy findings. In ten patients (3%), the physician would not rule out the possibility of MGRS but would consider a kidney biopsy only if kidney function or proteinuria worsened. In eight patients (2%), biopsy was deferred because the patients were deemed not to be candidates for therapy due to poor functional status even if an MGRS lesion were to be identified on kidney biopsy (Figure 3). Taken together, in 20% of the patients, kidney biopsy was deferred because it would not have changed management.

Of the 180 patients that were not seen by a nephrologist or a hematologist, the majority were seen by a primary care provider or a cardiologist (Supplemental Figure 2). When evaluating the baseline characteristics, patients that saw a nephrologist and/or a hematologist had a higher baseline serum creatinine, proteinuria, M-spike, and a higher percentage of patients with abnormal FLC compared with those patients that were not referred (Supplemental Table 3). When evaluating the underlying comorbidities between the two groups, the overall CCI score was similar. However, there was a higher rate of active malignancy and coronary artery disease in patients who were not referred to a specialist (Supplemental Table 3).

Rate and Predictors of Performing a Kidney Biopsy in Patients with CKD and MG (2017–2018)

We next compared patients’ baseline demographics, clinical characteristics, and underlying comorbidities (based on CCI score) between the patients that underwent a kidney biopsy and those who did not. Patients who underwent a kidney biopsy were significantly younger, had a higher serum creatinine, and higher proteinuria and hematuria on urinalysis compared with those who did not undergo a kidney biopsy in univariate analysis. There were no differences between the two groups with respect to the type of heavy chain, serum FLC ratio, or serum M-spike (Table 3). There was also no difference between the two groups when comparing the underlying comorbidities based on CCI score (3.3 in the kidney biopsy group and 3.8 in the nonbiopsy group, P=0.08) (Supplemental Table 4). When evaluating the individual comorbidities, congestive heart failure lowered the odds of undergoing a kidney biopsy (OR, 0.46; 95% CI, 0.23 to 0.90) (Supplemental Table 4). In this subgroup of patients with
congestive heart failure who did not undergo a kidney biopsy (n=171), biopsy was deferred due to poor functional status in six patients. In 42 patients, biopsy was deferred because they had known AL-amyloidosis. In the majority of the other patients, biopsy was not pursued because there was low suspicion for MGRS.

In the multivariate analysis, younger age, higher serum creatinine, and higher degree of proteinuria at the time of biopsy independently predicted the odds of performing a kidney biopsy among patients with CKD and MG. On the other hand, sex, hematuria, and presence of abnormal FLC did not increase the odds of performing renal biopsy (Table 4).

**Hematologic Workup in Patients with CKD and MG Who Did Not Undergo a Kidney Biopsy (2017–2018)**

In certain patients (mainly those with AL-amyloidosis), the diagnosis can be made in the absence of a kidney biopsy and is based on another tissue diagnosis instead (e.g., BM biopsy). Therefore, we reviewed the records of patients who saw a hematologist (n=264) to find out what type of hematologic workup was completed that may have resulted in deferring a kidney biopsy.

**Figure 2.** Study flowchart of patients with CKD and MG between 2017 and 2018.

**Figure 3.** Rationales for not referring or pursuing a kidney biopsy in a patient with CKD and MG (if seen by a hematologist and/or nephrologist). *A total of 61 patients were diagnosed with AL-amyloidosis and one patient was diagnosed with high risk smoldering myeloma.
kidney biopsy. Of the 264 patients, 75 did not have any additional workup completed, 153 underwent a BM biopsy, 114 had a fat aspirate, and eight patients had other tissue biopsies (Figure 4). This workup resulted in the diagnosis of AL-amyloidosis in 61 patients (53 based on either BM, fat aspirate, or both, and eight based on other tissue biopsy) and diagnosis of smoldering myeloma in one patient (whom the hematologist decided to treat).

DISCUSSION

Over the last decade, MG has been increasingly recognized as a potential cause of kidney damage. The term MGRS has been coined to highlight the fact that monoclonal proteins (in the absence of a hematologic malignancy requiring treatment) can indeed cause kidney disease for which therapy is indicated, and to differentiate this entity from MG of undetermined significance in which the monoclonal protein is of no immediate clinical significance. However, thus far, the rate and clinical predictors of finding an MGRS lesion on kidney biopsy specimen have not been evaluated. Our study is the first to show that, in patients with a positive monoclonal study, the rate of performing a kidney biopsy is quite low at 2.5%. This rate increases to 10% in the CKD population, but overall remains low. In patients that do undergo a kidney biopsy, the likelihood of finding a lesion that is unrelated to the monoclonal protein is up to 60% with arteriosclerosis and diabetic nephropathy accounting for up to 40% of non-MGRS lesions.
This is not surprising because both are the leading causes of ESKD in the population of the United States. The majority of the patients who were biopsied were older, male, and white. This reflects the fact that both CKD and MG are prevalent among this population and, therefore, they can be concomitantly present in a patient without a direct causal relationship between the two.

Among the MGRS group, AL-amyloidosis was the most common finding on kidney biopsy specimens and accounted for almost half of all of the lesions. Indeed, when evaluating the reasons as to why a kidney biopsy was deferred in patients with known CKD and MG, an established diagnosis of AL-amyloidosis accounted for 18% of the patients (n=61). This rate may be even higher because not all patients in our cohort with MG were referred to a hematologist and/or a nephrologist or had a full hematologic workup completed. A notable clinical difference in the amyloid group compared with the nonamyloid MGRS group was that patients with AL-amyloidosis had lower systolic and diastolic BPs. The lower BP at the time of diagnosis may be a reflection of potential autonomic involvement in some of the patients with amyloidosis. Certainly the finding of low BP in a patient with MG and proteinuria should raise suspicion for underlying amyloidosis and a kidney biopsy should be highly considered (unless the diagnosis is already apparent from another tissue biopsy). PGNMID was the second most common kidney biopsy specimen finding. This rate is higher than previously reported. This is likely due to the fact that the previous studies that have evaluated the association between monoclonal protein and kidney disease were done before PGNMID was widely recognized as an entity.

Of the nonhematologic clinical factors, urine studies were the most helpful in predicting which patient was likely to have an MGRS lesion. Indeed, urinary protein $\geq 1.5 \text{ g/d}$ and hematuria at the time of kidney biopsy significantly increased the odds of finding an MGRS lesion. This is not entirely surprising because the presence of blood and protein in the urine is a reflection of glomerular damage and inflammation which can result from the monoclonal protein. Urinalysis should also be evaluated for presence of glycosuria in addition to proteinuria because two thirds of the patients with LCPT had evidence of glycosuria in addition to proteinuria in our cohort. Lower C3 complement level was also associated with increased risk of finding an MGRS lesion. This finding signifies the effect of monoclonal protein on complement activation, particularly the alternate complement pathway. Indeed, both patients with C3 GN and MG in our cohort had low C3 levels, suggestive of activation of the alternative complement pathway.

Of the hematologic parameters, the strongest predictor of finding an MGRS lesion in the multivariate analysis was the finding of an abnormal FLC, with higher FLC levels increasing the likelihood of finding such a lesion. The lesions more commonly identified included AL-amyloidosis, LCPT, and light chain deposition disease. In patients with AL-amyloidosis,
not surprisingly, the λ light chain levels were also higher which is consistent with prior reports.\(^{18,19}\) M-spike and non-IgG heavy chains have been shown to increase the risk of progression to MM, however, they did not increase the risk of finding an MGRS lesion in our cohort. This may be because, in patients with MGRS, it is not the amount of protein that increases the risk of finding an MGRS lesion, but rather the innate characteristics of the protein.\(^{3,20}\) Another notable finding associated with increased risk of MGRS lesion was an abnormal BM biopsy specimen. The higher the percentage of abnormal plasma cells, the more likely it was that the patient would have an MGRS lesion. This is in contrast to patients with MGRS that do not have monoclonal protein detectable in the blood who typically have a normal BM biopsy specimen.\(^{21}\)

In patients with detectable monoclonal protein in the blood, having an abnormal BM biopsy specimen significantly increased the odds of having an MGRS lesion on the kidney biopsy sample. We therefore recommend checking serum FLC and considering a BM biopsy in patients with CKD who also have positive serum protein electrophoresis/serum immunofixation or urine protein electrophoresis/urine immunofixation because, if both are abnormal, the likelihood of finding an MGRS lesion is high and a kidney biopsy should be considered (Supplemental Figure 3).

We further evaluated the 37 patients with DM and MG who underwent a kidney biopsy to identify factors that may increase the likelihood of finding an MGRS lesion. We focused on this group because DM is a leading cause of CKD and is commonly associated with proteinuria. Therefore, identifying patients that would benefit from a kidney biopsy in the setting of MG can be a clinical challenge. In this population, only 20% of biopsy specimen findings were related to the monoclonal protein. In the MGRS group, however, proteinuria was significantly higher and was the only clinical parameter to increase the odds of finding an MGRS lesion. Indeed, the lowest proteinuria level in the diabetic group with MGRS lesions was about 0.86 g/d. Interestingly, the serum creatinine or baseline hemoglobin A1c were not predictive. The most common MGRS lesion was AL-amyloidosis similar to the overall cohort.

Given the decision as whether to refer a patient with MG and CKD to a specialist and whether to perform a kidney biopsy is inherently biased and dependent on the clinical decision making by the physician that is treating the patient at the time, we decided to further evaluate what percentage of patients with underlying CKD and MG underwent a kidney biopsy and to further delineate the reasons as to why a biopsy or a referral to a specialist may have been deferred. Among the 1608 patients with positive monoclonal studies, up to 37% had evidence of underlying CKD but only 10% of those with CKD had a kidney biopsy. This was despite the fact that the majority of the patients (70%) were seen by either a hematologist or a nephrologist. The patients with CKD that were not referred to a specialist did have a lower serum creatinine, lower proteinuria, lower M-spike, and fewer patients had an abnormal FLC ratio, suggesting a hematology or nephrology referral was not pursued either due to lack of awareness that the patient had CKD or the CKD and the MG were deemed "mild." The patients who were not referred to a specialist did have a higher rate of active malignancy and coronary artery disease, which raises the possibility that a referral may have been deferred because the treating physician deemed the patient to be a poor candidate for biopsy and/or treatment. However, when specifically evaluating the patients that saw either a hematologist or a nephrologist, poor functional status accounted for a very small proportion of the overall cohort (2%). This was consistent with the fact that the overall comorbidities (CCI score) were similar between the patients that had a kidney biopsy versus those that did not. In addition, the CCI score in our cohort of patients with CKD was similar to what has previously been reported in patients with CKD.\(^{22}\) Taken together, in the majority of the patients (80%), the main reason for deferring the biopsy was either lack of awareness or low suspicion for MGRS. In only 20% of patients was a nephrology referral or a kidney biopsy deferred because the kidney biopsy was unlikely to change management, either because the diagnosis was already known or the patient was not a candidate for treatment.

The rate of CKD among the patients with MG in our cohort is similar to the previous report by Burwick et al.\(^{23}\) In their cohort of Veterans Affairs patients, 44% of patients with MG had eGFR <60 ml/min per 1.73 m\(^2\). The rate in that study was slightly higher likely due to the fact that they also included patients with MM and those on dialysis in their cohort.\(^{23}\) Clinical factors that increased the likelihood of performing a kidney biopsy included younger age, elevated serum creatinine, and higher proteinuria at the time of kidney biopsy, despite the fact that age and baseline creatinine are not important predictors of having an MGRS lesion. Similarly, affected to unaffected FLC ratio did not influence the odds of receiving a kidney biopsy among patients with CKD and MG. This suggests that nephrologists do not take into account the importance of abnormal FLC when deciding whom to biopsy, despite the fact that it is predictive of finding an MGRS lesion.

The current consensus guideline on management of suspected MGRS suggests that clinicians should comprehensively evaluate the patient and their renal function and nephrologists should have a low threshold to perform a kidney biopsy.\(^{3}\) We agree with these recommendations. With respect to kidney parameters, the degree of proteinuria and hematuria are most helpful and should be formally evaluated in all patients. Based on our findings, it would also be important for patients to have a comprehensive hematologic workup completed because having an abnormal FLC and BM biopsy specimen significantly increases the odds of having an MGRS lesion.

Our study has several strengths. First, our cohort is unique because we excluded patients with hematologic conditions that required specific treatment (MM, CLL, and other lymphomas) and it therefore allowed us to study the true rate of MGRS. Second, we evaluated the patients with CKD and MG
to assess what predicts who undergoes a kidney biopsy because our cohort is retrospective and the decision on whom to biopsy can be biased. We also looked to see why a biopsy may have been deferred. Third, our sample size was relatively large which allowed us to observe and capture statistical differences. Despite several strengths, our study has several limitations. Our cohort was based on a single tertiary center resulting in a referral bias. In addition, most of the patients in our cohort were white which may limit generalizability. Lastly, we were not able to fully evaluate the reasons as to why monoclonal studies were ordered in the first place. Monoclonal studies are typically ordered at our institution for a specific indication such as evaluation of anemia, CKD, proteinuria, or autonomic neuropathy and are not ordered as a matter of routine testing. Thus the underlying inherent selection bias cannot be addressed in this study.

In conclusion, in patients with MG who undergo a kidney biopsy, the rate of finding an MGRS lesion was about 40% with AL-amyloidosis and PGNMID representing the majority of the cases. Proteinuria ≥1.5 g/dl, hematuria, low serum C3 levels, abnormal FLC, and abnormal BM biopsy specimen all increased the odds of finding an MGRS lesion on the kidney biopsy sample.

DISCLOSURES

N. Leung reports grants from Omeros, outside the submitted work. N. Leung is on an advisory board for AbbVie and Takeda. All remaining authors have nothing to disclose.

ACKNOWLEDGMENTS

We would like to thank Lisa Vaughan who advised on the statistical method and Dr. Angela Dispenzieri who helped provide the cohort of patients with positive monoclonal studies from the Mayo Clinic Laboratory Database. Dr. Nattawat Klomjit and Dr. Ladan Zand designed the study, did data abstraction, performed statistical analysis, and drafted and revised the manuscript. Dr. Nelson Leung, Dr. Fernando Fervenza, and Dr. Sanjeev Sethi drafted and revised the manuscript.

SUPPLEMENTAL MATERIAL

This article contains the following supplemental material online at http://jasn.asnjournals.org/lookup/suppl/doi:10.1681/ASN.2020010054/-/DCSupplemental.

Supplemental Figure 1. Hematological workup in patients with AL-amyloidosis with kidney involvement between 2013 and 2018.

REFERENCES


Supplemental Figure 2. Referral pattern in CKD patients with monoclonal gammopathy without a kidney biopsy from 2017 to 2018.

Supplemental Figure 3. Algorithm for approaching patients with CKD and monoclonal gammopathy.

Supplemental Table 1. Characteristics of diabetic patients who had a kidney biopsy between 2013 and 2018.

Supplemental Table 2. Baseline characteristics and comorbidities of CKD patients with monoclonal gammopathy in the absence of a kidney biopsy who were seen by a nephrologist/hematologist versus other providers.

Supplemental Table 3. Comorbidities among CKD patients with monoclonal gammopathy in 2017 and 2018.

Supplemental Table 4. Baseline characteristics comparing patients with amyloidosis-MGRS and non-amyloidosis MGRS between 2013 and 2018.


