Standardized Reporting of Monoclonal Immunoglobulin-Associated Renal Diseases: Recommendations from a Mayo Clinic/Renal Pathology Society Working Group

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Key words: Monoclonal immunoglobulin, kidney biopsy glomerulonephritis, monoclonal gammopathy of renal significance

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The term monoclonal gammopathy refers to the overproduction of a monoclonal immunoglobulin (MIg) that is detectable in the serum, urine, or tissue resulting from the clonal proliferation of immunoglobulin (Ig)-producing plasma cells or B lymphocytes.[1] The term monoclonal gammopathy of undetermined significance (MGUS) is applied when a MIg is detected in the absence of plasma cell or lymphoid malignancy or end organ damage, and implies a "benign" condition. [1, 2]

The MIg originating as result of malignant or premalignant/non-malignant disease may then result in kidney disease.[3] The term monoclonal gammopathy of renal significance (MGRS) was originally introduced to acknowledge a clonal plasma cell or B cell population causing a renal lesion, in the absence of a hematologic malignancy or other myeloma defining events (MGRS = MGUS + MIg-related renal disease); the renal lesion is nonetheless a consequence of the MIg, which carries major implications for management and prognosis.[4, 5] The term was later modified to acknowledge clonal plasma cell or B cell proliferative disorders that do not require immediate treatment for the clonal disease including smoldering myeloma and some low grade lymphomas such as CLL.[6] Conceptually, MGRS is neither a specific renal disease nor a specific hematologic disorder. Its usage has facilitated the adoption of therapies directed at the clonal proliferation, which hematologists had historically been reluctant to treat.

A kidney biopsy is required to diagnose renal disease that is mediated either directly or indirectly by the MIg. Typically, 4 scenarios can occur:

- The patient has a detectable serum/urine MIg, but no renal disease associated with MIg is identifiable.
- The patient has a detectable serum/urine MIg, and a renal disease related to intrarenal deposition of MIg is identified.
- The patient has a detectable serum/urine MIg, and a renal disease indirectly associated with MIg is identified.
- The patient has no detectable serum/urine MIg, yet a renal disease related to deposition of MIg is identified.

A meeting sponsored by the Renal Pathology Society was organized on June 8th, 2019, at the Mayo Clinic, Rochester, MN to address the studies required to confirm the MIg-related renal disease by kidney biopsy, and standardization of the kidney biopsy report in these patients.

Studies required for confirmation of monoclonal Ig deposits in the kidney biopsy

Immunofluorescence (IF) studies using antibodies to IgG, IgM, IgA, kappa and lambda are mandatory to detect MIg deposits in the kidney. Immunohistochemistry (IHC) using antibodies to IgG, IgM, IgA,

kappa and lambda may be performed as an alternative to IF. Although the majority of MIg deposits will be revealed, a very small subset of heavy chain IgD or IgE MIg will be missed by a routine IF panel. In patients with monoclonal IgG deposits, IgG subclass staining is recommended. The rational for IgG subtyping is important for the following reasons: 1. It confirms the monotypic deposits; 2. The finding of IgG3 (most common) versus IgG1 (second most common) has important clinical implications. IgG1 is generally associated with a detectable serum monoclonal Ig and a lymphoproliferative disorder that may respond to specific targeted treatment. On the other hand, a monoclonal Ig/lymphoproliferative disease is less likely to be detected in the setting of IgG3 deposits.

A Congo red (amyloid) stain is strongly advised in all patients with a serum/urine MIg. All MIg detected by kidney biopsies should be correlated with serum and urine tests for MIg.

It is suggested that IF studies for immunoglobulins and light chains be performed on protease digested, paraffin embedded tissue section (paraffin IF) in all cases of apparent C3 glomerulopathy (C3G) with a circulating MIg to enable detection of masked MIg deposits.[3, 7] Paraffin IF is also recommended when the differential diagnosis includes a light chain proximal tubulopathy. Immunohistochemical stains for light chains may also be useful in detecting intracellular MIg where routine and pronase studies are negative. Finally, paraffin IF may also be beneficial for renal lesions with detectable deposits by electron microscopy (EM) but where the routine IF is negative or equivocal.

Mass spectrometric analysis of laser microdissected kidney tissue containing Congo red positive deposits is suggested to type amyloidosis when the findings by IF and/or immunohistochemistry are equivocal.

Standardization of the kidney biopsy report

The patient has a detectable serum/urine MIg, but no renal disease associated with MIg is identifiable: In such cases (1) or (2) is recommended and should be highlighted in the report:

1. In the diagnosis: No evidence of a MIg-related lesion is identified.
2. In a comment, immediately following the diagnosis: There is no evidence for a renal lesion related to the patient's MIg in this biopsy.

The patient has a detectable serum/urine MIg, and a renal disease related to deposition of MIg is identified: For such lesions the biopsy report should follow the standardized reporting suggested in the RPS classification and reporting of glomerular diseases.[8]

Thus, the report should include the primary diagnosis such as cast nephropathy, AL amyloidosis, monoclonal immunoglobulin deposition disease (MIDD), cryoglobulinemic glomerulonephritis, proliferative glomerulonephritis with MIg deposits (PGNMID), light chain proximal tubulopathy, immunotactoid glomerulonephritis, etc. In some cases, multiple renal diseases related to the MIg may be present such as cast nephropathy plus MIDD or AL amyloidosis; each disease entity should then be listed. The type of MIg (e.g., kappa light chains) should be specified in the primary diagnosis, as should the extent of involvement (glomeruli, tubular basement membranes, interstitium, arterioles, arteries) in cases of AL amyloidosis. Where appropriate, the primary diagnosis should be followed by the pattern of glomerular injury such as membranoproliferative glomerulonephritis, focal or diffuse endocapillary proliferative glomerulonephritis, mesangial proliferative glomerulonephritis, membranous glomerulopathy, etc. Finally, additional findings should include the extent of chronic changes (glomerulosclerosis, tubular atrophy and interstitial fibrosis, arteriosclerosis and hyaline arteriosclerosis) and other findings such as interstitial nephritis and acute tubular injury. The calculation of a chronicity score is endorsed.[9]

The association of the patient's known hematologic condition with the MIg-associated renal disease should be made in the comment section. If a hematologic disease is known it should be correlated with the renal disease (e.g., MIDD associated with multiple myeloma/clinical, AL amyloidosis associated with MGRS/clinical, etc.). In cases where an underlying cause of the MIg is not known an appropriate work-up should be recommended.

The patient has a detectable serum/urine MIg, and a renal disease indirectly associated with MIg is identified: This includes C3G and thrombotic microangiopathy (TMA) where the MIg is thought to activate the alternative pathway of complement, thereby causing renal disease. The biopsy report should follow the standardized reporting with a primary diagnosis of C3G or TMA, followed by pattern of injury, and additional findings. The association of C3G and TMA with MIg should be reported in the comment section, as should any underlying hematologic disease (or recommended work-up for one) as specified above. Evaluation of other non-MIg causes of C3G and TMA should also be recommended. The calculation of a chronicity score is endorsed.[9]

The patient has no detectable serum/urine MIg, yet a renal disease related to deposition of MIg is identified: This most typically includes the entity of PGNMID; additionally in rare cases of AL amyloidosis and MIDD a MIg may not be detected. The biopsy report should follow standardized

reporting and a comment should suggest that MIg is the likely cause of the renal disease and a thorough evaluation for MIg is recommended. The calculation of a chronicity score is endorsed.[9]

Examples of the kidney biopsy diagnosis in varying scenarios are provided in Table 1.

In conclusion, we provide a summary of clinical and pathologic scenarios seen in patients with renal disease and a MIg in the serum/urine, kidney, or both, as well as recommendations for optimal reporting of the renal biopsy findings. We believe that the suggested format for reporting kidney biopsy findings will provide the optimal information to nephrologists and hematologists who rely on the kidney biopsy report as they order additional tests and develop a treatment strategy. While the term MGRS has been useful to spur coordinated efforts between hematologists and nephrologists in the work-up of these patients, it must be stressed that MGRS is not a specific diagnosis per se and should not be used by the renal pathologist as a primary diagnostic entity.

Conflicts of interest: None

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Table 1. Examples of Renal Biopsy Diagnoses in Patients with MIg-Related Kidney Lesions

1. Primary diagnosis: 1) Diabetic nephropathy, advanced with nodular glomerulosclerosis. 2) No evidence of a monoclonal immunoglobulin-related lesion is identified**.**

Ancillary studies: Congo red stain is negative for amyloidosis.

Additional findings: Focal (60%) global glomerulosclerosis, extensive (70%) tubular atrophy and interstitial fibrosis, severe arteriosclerosis. Chronicity index: Severe (10/10)

2. Primary diagnosis: Light chain cast nephropathy, kappa type

Pattern of injury: Acute tubular injury with approximately 10% of tubules involved by light chain casts

Additional findings: Focal (20%) global glomerulosclerosis, mild (20%) tubular atrophy and interstitial fibrosis, moderate arteriosclerosis. Chronicity index: Mild (4/10)

Ancillary studies: Congo red stain is negative for amyloidosis.

Comment: The findings are consistent with patient's documented multiple myeloma. Cast nephropathy is a myeloma defining event.

3. Primary diagnosis: Light chain deposition disease, kappa type

Pattern of injury: Nodular sclerosing glomerulopathy

Additional findings: Focal (30%) global glomerulosclerosis, moderate (30%) tubular atrophy and interstitial fibrosis, mild arteriosclerosis. Chronicity index: Moderate (6/10)

Ancillary studies: Congo red stain is negative for amyloidosis.

Comment: The findings are consistent with patient's documented multiple myeloma.

4. Primary diagnosis: AL amyloidosis, lambda light chain type, involving the glomeruli, interstitium and vessels

Additional findings: Focal (10%) global glomerulosclerosis, mild (20%) tubular atrophy and interstitial fibrosis, moderate arteriosclerosis. Chronicity index- Mild (4/10)

Ancillary studies: Congo red stain is positive.

Comment: The findings are consistent with patient's documented multiple myeloma.

5. Primary diagnosis: Kappa light chain proximal tubulopathy

Additional findings: Focal (10%) global glomerulosclerosis, mild (20%) tubular atrophy and interstitial fibrosis, moderate arteriosclerosis. Chronicity index- Mild (4/10)

Ancillary studies: Congo red stain is negative.

Comment: Clinical correlation with hematologic studies is recommended.*

*(In this case hematologic findings were not available at the time of kidney biopsy)

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6. Primary diagnosis: Proliferative glomerulonephritis with monoclonal immunoglobulin deposits, IgG3-kappa type

Pattern of injury: Membranoproliferative glomerulonephritis

Additional findings: Focal (20%) global glomerulosclerosis, moderate (30%) tubular atrophy and interstitial fibrosis, mild arteriosclerosis. Chronicity index: Moderate (5/10)

Ancillary studies: Congo red stain is negative for amyloidosis. IgG subtypes show IgG3 subtype restriction.

Comment: Serum/urine studies are negative for a monoclonal immunoglobulin. While such negative findings are frequent in patients with proliferative glomerulonephritis with monoclonal immunoglobulin deposits, the glomerulonephritis in such cases is nonetheless considered to result from deposition of a monoclonal immunoglobulin.

7. Primary diagnosis: C3 glomerulonephritis

Pattern of injury: Membranoproliferative and sclerosing glomerulonephritis with focal (10%) cellular crescents

Additional findings: Focal (30%) global glomerulosclerosis, moderate (30%) tubular atrophy and interstitial fibrosis, mild arteriosclerosis. Chronicity index: Moderate (6/10)

Ancillary studies: Congo red stain is negative for amyloidosis. Pronase immunofluorescence studies are negative for masked immunoglobulin or light chain deposits.

Comment: Serum immunofixation studies are positive for a monoclonal immunoglobulin. Monoclonal immunoglobulin has been shown to be associated with C3 glomerulonephritis.

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Examples of the kidney biopsy diagnosis in varying scenarios are provided in Table 1.

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Ancillary studies: Congo red stain is negative for amyloidosis.

Additional findings: Focal (60%) global glomerulosclerosis, extensive (70%) tubular atrophy and interstitial fibrosis, severe arteriosclerosis. Chronicity index: Severe (10/10)

2. Primary diagnosis: Light chain cast nephropathy, kappa type

Pattern of injury: Acute tubular injury with approximately 10% of tubules involved by light chain casts

Additional findings: Focal (20%) global glomerulosclerosis, mild (20%) tubular atrophy and interstitial fibrosis, moderate arteriosclerosis. Chronicity index: Mild (4/10)

Ancillary studies: Congo red stain is negative for amyloidosis.

Comment: The findings are consistent with patient's documented multiple myeloma. Cast nephropathy is a myeloma defining event.

3. Primary diagnosis: Light chain deposition disease, kappa type

Pattern of injury: Nodular sclerosing glomerulopathy

Additional findings: Focal (30%) global glomerulosclerosis, moderate (30%) tubular atrophy and interstitial fibrosis, mild arteriosclerosis. Chronicity index: Moderate (6/10)

Ancillary studies: Congo red stain is negative for amyloidosis.

Comment: The findings are consistent with patient's documented multiple myeloma.

4. Primary diagnosis: AL amyloidosis, lambda light chain type, involving the glomeruli, interstitium and vessels

Additional findings: Focal (10%) global glomerulosclerosis, mild (20%) tubular atrophy and interstitial fibrosis, moderate arteriosclerosis. Chronicity index- Mild (4/10)

Ancillary studies: Congo red stain is positive.

Comment: The findings are consistent with patient's documented multiple myeloma.

5. Primary diagnosis: Kappa light chain proximal tubulopathy

Additional findings: Focal (10%) global glomerulosclerosis, mild (20%) tubular atrophy and interstitial fibrosis, moderate arteriosclerosis. Chronicity index- Mild (4/10)

Ancillary studies: Congo red stain is negative.

Comment: Clinical correlation with hematologic studies is recommended.*

*(In this case hematologic findings were not available at the time of kidney biopsy)

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6. Primary diagnosis: Proliferative glomerulonephritis with monoclonal immunoglobulin deposits, IgG3-kappa type

Pattern of injury: Membranoproliferative glomerulonephritis

Additional findings: Focal (20%) global glomerulosclerosis, moderate (30%) tubular atrophy and interstitial fibrosis, mild arteriosclerosis. Chronicity index: Moderate (5/10)

Ancillary studies: Congo red stain is negative for amyloidosis. IgG subtypes show IgG3 subtype restriction.

Comment: Serum/urine studies are negative for a monoclonal immunoglobulin. While such negative findings are frequent in patients with proliferative glomerulonephritis with monoclonal immunoglobulin deposits, the glomerulonephritis in such cases is nonetheless considered to result from deposition of a monoclonal immunoglobulin.

7. Primary diagnosis: C3 glomerulonephritis

Pattern of injury: Membranoproliferative and sclerosing glomerulonephritis with focal (10%) cellular crescents

Additional findings: Focal (30%) global glomerulosclerosis, moderate (30%) tubular atrophy and interstitial fibrosis, mild arteriosclerosis. Chronicity index: Moderate (6/10)

Ancillary studies: Congo red stain is negative for amyloidosis. Pronase immunofluorescence studies are negative for masked immunoglobulin or light chain deposits.

Comment: Serum immunofixation studies are positive for a monoclonal immunoglobulin. Monoclonal immunoglobulin has been shown to be associated with C3 glomerulonephritis.

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