Monoclonal gammopathy of renal significance (MGRS): when MGUS is no longer undetermined or insignificant

Nelson Leung1,2, Frank Bridoux3, Colin A Hutchison4, Samih H Nasr5, Paul Cockwell4, Jean-Paul Fermand6, Angela Dispenzieri2, Kevin W Song7, Robert A Kyle2 on behalf of the International Kidney and Monoclonal Gammopathy Research Group

Key words: monoclonal gammopathy, myeloma, renal, glomerulonephritis

Corresponding author:

Nelson Leung

200 First Street SW

Rochester MN 55905

507-266-7083

Fax: 507-266-7891

leung.nelson@mayo.edu
Abstract

Multiple myeloma (MM) is the most frequent monoclonal gammopathy to involve the kidney; however, a growing number of kidney diseases associated with other monoclonal gammopathies are being recognized. Although many histopathologic patterns exist, they are all distinguished by the monoclonal immunoglobulin (or component) deposits. The hematologic disorder in these patients is more consistent with monoclonal gammopathy of undetermined significance (MGUS) than with MM. Unfortunately due to the limitations of the current diagnostic schema, they are frequently diagnosed as MGUS. Since treatment is not recommended for MGUS, appropriate treatment is commonly withheld. In addition to end stage renal disease and the persistence of the monoclonal gammopathy is associated with high rates of recurrence after kidney transplantation. Preservation and restoration of kidney function is possible upon successful treatment targeting the responsible clone. Achievement of hematologic complete response has been shown to prevent recurrence after kidney transplantation. There is a need for a term that properly conveys the pathologic nature of these diseases. We feel the term monoclonal gammopathy of renal significance (MGRS) is most helpful to indicate a causal relationship between the monoclonal gammopathy and the renal damage and since the significance of the monoclonal gammopathy is no longer undetermined.
Monoclonal gammopathy of undetermined significance (MGUS) is a condition characterized by the presence of a monoclonal gammopathy without end organ damage.\(^1\) MGUS requires the serum monoclonal (M) protein and bone marrow plasma cells to be less than 3 g/dL and 10% respectively. Most importantly there can be no end organ damage attributable to the plasma cell dyscrasia. Although MGUS is considered a precursor to multiple myeloma (MM), the risk of progression to MM, lymphoproliferative disorder or immunoglobulin light chain (AL) amyloidosis is low which on average is 1%/year.\(^2,3\)

Smoldering multiple myeloma (SMM) is defined by a serum M-protein > 3 g/dL or > 10% bone marrow involvement by clonal plasma cells in the absence of end organ damage.\(^2\) The risk of developing MM or AL amyloidosis is significantly higher in patients with SMM as compared to MGUS ranging from 51% at 5 years, 66% at 10 years to 73% at 15 years. Treatment is not recommended until progression to MM which is characterized by CRAB (hypercalcemia, renal impairment, anemia, bone disease) because some patients can remain asymptomatic for years.\(^2,4-6\)

Renal impairment is a defining criterion of MM. Aside from a serum creatinine > 2.0 mg/dl attributable to the plasma cell dyscrasia, the current guidelines do not define the renal disease any further.\(^2,7\) Cast nephropathy, acute tubular necrosis (ATN) due to hypercalcemia or non steroidal antiinflammatory drugs (NSAIDs), AL amyloidosis, monoclonal immunoglobulin deposition disease of the Randall type (MIDD) and light chain proximal tubulopathy (with or without Fanconi Syndrome) have all been described with MM.\(^8-10\) Other than cast nephropathy and hypercalcemia, MM is not required for the development of the other kidney diseases.

In fact, a growing number of pathologic renal conditions are being attributed to a clonal plasma cell disorder which is less “myeloma-like” and more “MGUS-like” in terms of its bulk and proliferative rate.\(^11,12\) Unfortunately, the current diagnostic schema fails to properly categorize the hematologic disorder in these patients. Since they do not meet conditions for SMM or MM, these patients are mistakenly diagnosed as MGUS. Terms such as” MIDD with MGUS” or “glomerulonephritis with MGUS” have been used in the literature and diagnosis.\(^13-15\) Unfortunately, MGUS in this context is
misrepresented because in these patients, *there is significance* to the monoclonal gammopathy; and its significance is not “undetermined.” As a matter of fact, despite their non-malignant nature, these diseases are associated with a great deal of morbidity and even mortality.\(^\text{10,12,16}\) MGUS should not be used to describe hematologic disorders that results in kidney disease. It is due to this necessity that we propose the term “monoclonal gammopathy of renal significance” (MGRS) to discriminate the pathologic nature of these diseases from the truly benign MGUS.

Evidence already supports monoclonal protein as the direct cause of the kidney disease and not the tumor. Bence-Jones proteins isolated from patients with paraprotein related kidney diseases are capable of replicating the kidney disease when injected into animals.\(^\text{17}\) In addition, only 15% of AL amyloidosis and 65% of MIDD patients meet criteria for MM.\(^\text{9,10}\) Thus the practice of using malignancy as a prerequisite for treatment in MGRS patients is unnecessary and inappropriate. Nevertheless, many of these patients either receive no treatment or are under-treated.\(^\text{18}\) In a large Italian study of MIDD patients, cytotoxic therapy was not prescribed to nearly 30% of those without MM.\(^\text{10}\) In those who were treated, none received vincristine-doxorubicin-dexamethasone (VAD) or vincristine-doxorubicin-methylprednisolone (VAMP), the standard therapy for MM at the time.\(^\text{19}\) Although the MGUS-like biology sometimes makes the hematologic disease less lethal, the effect on the kidney regrettably is not as benign. A study of 19 MIDD patients (63% with “MGUS”) found the 1 year and 5 years patient survival to be 89% and 70% while the renal survival was only 67% and 37% for the corresponding periods.\(^\text{20}\) The high rate of end stage renal disease (ESRD) was attributed to the absent or inadequate chemotherapy.

In addition to AL amyloidosis, MIDD and light chain proximal tubulopathy, there are a number of renal diseases now recognized to be associated with MGRS (Table 1). Proliferative glomerulonephritis with monoclonal IgG deposits (PGNMIID) is characterized by monoclonal immunoglobulin deposits (most commonly IgG3\(\kappa\)) that results in a proliferative or membranoproliferative pattern of injury. These patients present with nephrotic range proteinuria and renal impairment.\(^\text{11}\) One large study found detectable monoclonal protein in 30% of patients but only 3% had evidence of MM. A monoclonal IgA
variant has been described. Recurrence of PGNMID frequently occurs after kidney transplantation which often results in rapid loss of the kidney allograft. So far, benefits of immunosuppression in PGNMID remain unclear. Another renal disease is immunotactoid glomerulopathy which is a rare but morphologically distinctive glomerular disease characterized by glomerular deposition of microtubules arranged in parallel arrays. By immunofluorescence, these microtubules stain for immunoglobulins, most commonly IgG. A monoclonal protein can be detected in majority of these patients. The histopathologic pattern is most similar to membranous or membranoproliferative glomerulonephritis (MPGN) or a mixture of the two. Hematologically, 50% patients have a lymphoma most commonly chronic lymphocytic leukemia (CLL). The presence of MM in these patients is rare. Treating the underlying lymphoproliferative disorder generally leads to remission of proteinuria and stabilizing of renal function. Immunotactoid glomerulopathy should not be confused with cryoglobulinemia which also presents with large fibrils (30-50 nm) but are composed of cryoglobulins. Of the three types of cryoglobulinemia, only type I and II are composed of monoclonal immunoglobulins. Type I is usually the result of a plasma cell dyscrasia while type II is caused by a lymphoma with plasmacytic differentiation although the most common cause of type II cryoglobulinemia in the world is hepatitis C. Type III is composed of polyclonal immunoglobulins and should not be associated with MGRS. In addition to cryoglobulinemia, the monoclonal IgM from lymphoplasmacytic lymphoma (Waldenstrom macroglobulinemia) can also result in kidney injury characterized by a mesangiocapillary glomerulonephritis.

Some kidney diseases are only occasionally associated with MGRS. Previously MPGN was only linked to infections, connective tissue disease, complement dysregulation and malignancies but was not thought to be associated with monoclonal gammopathy. However, a recent study of 68 MPGN patients which excluded positive hepatitis (B & C) serology, dense deposit disease (Type II MPGN) and those without a monoclonal protein study found 41.1% had a monoclonal protein by serum and/or urine immunofixation. Monoclonal deposits identical to the circulating paraprotein were found in the
glomeruli of nearly every patient. Bone marrow biopsies obtained on the 28 patients showed a variety of pathology including “MGUS” (16), MM (6), low grade B-cell lymphoma (3), chronic lymphocytic leukemia (2) and lymphoplasmacytic lymphoma/Waldenström’s macroglobulinemia (1). Long term follow-up of the patients with “MGUS” revealed 2 later progressed to MM and 1 to CLL.

Kidney diseases with MGRS differ from those without MGRS in their recurrence rates. In a study of 29 patients with recurrent MPGN after kidney transplantation, 6 were found to have a circulating monoclonal protein and 1 had monoclonal deposits in the kidney. The recurrence rate was 71.4% in these 7 patients vs 29.1% in patients without a detectable monoclonal gammopathy, p = 0.14. While the small numbers failed to achieve statistical significance, this pattern is seen repeatedly in other MGRS kidney diseases. In a single center study, 5 of 7 (71.4%) patients with MIDD developed recurrence after kidney transplantation. The median time to recurrence was 33 months which nearly always resulted in graft loss. The risk of recurrence was associated with the presence of a monoclonal protein at the time of transplantation but not the plasma cell burden. Results were nearly identical to a review of 7 MIDD patients where 6 developed recurrence disease in the renal allograft. Similarities were also noted in transplant recipients with fibrillary glomerulonephritis. In a study of 12 patients who had 15 allografts, no recurrence was detected in any of the allografts in patients without a monoclonal gammopathy. In contrast, 6 of the 10 allografts in (7) patients with monoclonal gammopathy had recurrence. Time to recurrence ranged from 3 to 87 months posttransplant. The high rates of recurrence in MGRS kidney diseases is one of the most menacing clinical features and is associated with significant morbidity.

MGRS kidney diseases are diagnosed by demonstration of monoclonal deposits in the kidney. A kidney biopsy is usually indicated for significant proteinuria and/or renal insufficiency but is even more important when a monoclonal gammopathy is present. Immunofluorescence study should be performed on all suspected cases. Monoclonal deposits can consist of monoclonal light chains, heavy chains or intact immunoglobulins. Restriction to a single class of light chain and/or heavy chain is mandatory.
Equivocal results should undergo further testing such as immunogold electron microscopy or proteomics via laser dissection tandem mass spectrometry. Monoclonal protein studies should be performed to match the monoclonal protein in circulation with the monoclonal deposits in the kidney. Since MGRS may exhibit low levels of circulating monoclonal protein, immunofixation should be performed along with protein electrophoresis as well as serum free light chain assay to increase sensitivity. Even when immunofixation is negative, an abnormal serum free light chain ratio can help identify the pathologic light chain involved in the kidney disease. Monoclonal protein studies should be performed on all patients with MGRS associated renal lesions even those that are only occasionally associated with MGRS. Next, the origin of the monoclonal protein should be identified. In the bone marrow, establishing clonality of plasma cells or lymphocytes is essential. The clone must exhibits the same light chain restriction as the circulating monoclonal protein and deposits in the kidney.

The treatment of MGRS related kidney diseases should be tailored to the clone responsible. In the past, part of the reticence for withholding treatment was that alkylators were the only anti-plasma cell therapies available. The fear of alkylator induced myelodysplastic syndrome overshadowed the fear of ESRD. With the advent of novel agents, this fear is much less warranted. In addition, the purpose of treatment should also be viewed differently. Because of the high risk of recurrence, many of these patients are forced into a life on dialysis. Therefore, the goal of treatment should not be limited to preservation of life but should include organ preservation. In selected patients, autologous stem cell transplantation (ASCT) has increased the median survival of patients with AL amyloidosis from ~18 months to over 5 years. Melphalan and dexamethasone has produced similar outcomes and may be more appropriate for high risk patients. Regimens containing novel agents such as cyclophosphamide, thalidomide and dexamethasone (CTD), bortezomib and dexamethasone, cyclophosphamide, bortezomib and dexamethasone (CyBoR-D) and others have also shown high response rates. The high and fast response rates of these therapies along with the lack of stem cell damage make them attractive therapeutic options but long term outcome data are lacking. Improvement in survival, preservation and restoration of
renal function can be attained in those who achieve hematologic response.\textsuperscript{50,51} Similar strategies have also been found to be effective in patients with MIDD.\textsuperscript{52} Similar benefits in regard to the kidney have been demonstrated in patients with MIDD who achieved hematologic complete response (CR).\textsuperscript{53-55} Lymphoma based regimens was found to be effective in 10 of 12 patients with fibrillary glomerulonephritis secondary to lymphoproliferative disorders.\textsuperscript{24}

Treatment of MGRS should be considered even after development of ESRD without other organ involvement if the patient is being considered for kidney transplantation. Hematologic stringent complete response (CR) is the goal of therapy. First, evidence suggests achievement of CR prevents recurrence after kidney transplantation. In MIDD, successful kidney transplantation without recurrence was reported in patients who achieved hematologic CR after ASCT.\textsuperscript{53} Similar results have been reported in AL amyloidosis. The recurrence rate of 19 patients was reduced to 10.5\% when kidney transplantation was performed in conjunction with ASCT or melphalan and dexamethasone.\textsuperscript{56} One recurrence actually occurred prior to definitive treatment. Both hematologic and kidney disease were controlled after a successful ASCT. Another ASCT treated patients had a recurrence 52 months after kidney transplant and was successfully treated with melphalan dexamethasone. Second, achievement of CR in patients with low plasma cell burden and MGUS like proliferative rates appears to be significantly more durable than what is achievable in MM. In a randomized study of single vs double ASCT, the relapse free survival in MM after tandem ASCT was 36 months.\textsuperscript{57} In another study, the median time to progression after ASCT was increased to 39 months from 21 months by the addition of lenalidomide as maintenance therapy after ASCT.\textsuperscript{58} In comparison, the median time to relapse was estimated at 12.7 years for AL amyloidosis patients who achieved a CR after single ASCT without maintenance. In this population, the median bone marrow plasma cell involvement was 5\%.\textsuperscript{59} Thus, in patients with low plasma cell burden and proliferative rates, achievement of CR may provide significant advantage in both patient and graft survival after transplantation.
In summary, MGRS related kidney diseases are the results of toxic monoclonal protein produced by dangerous small B-cell clones. These disorders do not require treatment from a "tumoral" point of view (i.e. their bulk and proliferative rate) but treatment is often mandatory and sometimes urgent to prevent renal deterioration. In the past, there was a reluctance to use chemotherapy in patients without myeloma or AL amyloidosis. Therapies with novel agents have lessened the risk of treatment. Recovery of renal function is possible with adequate hematologic response. Even in patients with ESRD, treatment may be appropriate if kidney transplantation is being considered. The time has come for a term that separates MM and MGUS from monoclonal gammopathies which result in renal damage. We feel the term “monoclonal gammopathy of renal significance (MGRS)” fulfills this role. The term MGUS should be limited to those cases where no connection to end organ damage can be demonstrated. Meanwhile, MGRS should be used when the monoclonal protein is playing a direct role in the kidney disease. This distinction will hopefully alert the physician to the seriousness of these conditions and clarify the role of chemotherapy.

**Authorship**

Contribution: NL, FB, CAH, SN, PC, JPF, AD, KWS and RAK designed and wrote the manuscript.

Conflict of Interest: FB received honoraria from Janssen and Amgen and research funding from Celgene. AD has been a consultant for Millennium and Research funding from Johnson and Johnson, Celgene and Millennium.
References


<table>
<thead>
<tr>
<th>Crystals</th>
<th>Organized</th>
<th>Non-organized (granular)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Fibrillar</td>
<td>Microtubular</td>
</tr>
<tr>
<td>Myeloma cast nephropathy</td>
<td>Light chain amyloidosis</td>
<td>Type I and type II cryoglobulinemic glomerulonephritis</td>
</tr>
<tr>
<td>Light chain proximal tubulopathy (with or without Fanconi's syndrome)</td>
<td>Non-amyloid</td>
<td>Immunotactoid GN/</td>
</tr>
<tr>
<td>Crystal-storing histiocytosis</td>
<td>Fibrillary GN*</td>
<td>GOMMID</td>
</tr>
</tbody>
</table>

Abbreviations: GN, glomerulonephritis; GOMMID, glomerulonephritis with organized microtubular monoclonal Ig deposits; MIDD, monoclonal immunoglobulin deposition disease; LCDD, LHCDD, HCDD, light-chain, light- and heavy-chain, heavy-chain, deposition disease. * mostly associated with polyclonal IgG deposits
Monoclonal gammopathy of renal significance (MGRS): when MGUS is no longer undetermined or insignificant

Nelson Leung, Frank Bridoux, Colin A. Hutchison, Samih H. Nasr, Paul Cockwell, Jean-Paul Fermand, Angela Dispenzieri, Kevin W. Song and Robert A. Kyle