

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

Nelson Leung,^{1,2} Frank Bridoux,³ Colin A. Hutchison,⁴ Samih H. Nasr,⁵ Paul Cockwell,⁴ Jean-Paul Fermand,⁶ Angela Dispenzieri,² Kevin W. Song,⁷ and Robert A. Kyle,² on behalf of the International Kidney and Monoclonal Gammopathy Research Group

¹Division of Nephrology and Hypertension, Mayo Clinic, Rochester, MN; ²Division of Hematology, Mayo Clinic, Rochester, MN; ³Department of Nephrology and Transplantation, University Hospital Poitiers, Poitiers, France; ⁴Renal Institute of Birmingham, University Hospital Birmingham and University of Birmingham, Birmingham, United Kingdom; ⁵Department of Laboratory Medicine and Pathology, Mayo Clinic, Rochester, MN; ⁶University Hospital St Louis, Paris, Ile De France, France; and ⁷Division of Hematology, Vancouver General Hospital, Vancouver, BC

Multiple myeloma 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 multiple myeloma. Unfortunately, due to

the limitations of the current diagnostic schema, they are frequently diagnosed as MGUS. Because treatment is not recommended for MGUS, appropriate therapy is commonly withheld. In addition to end-stage renal disease, the persistence of the monoclonal gammopathy is associated with high rates of recurrence after kidney transplantation. Preservation and restoration of kidney function are possible with 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 think the term monoclonal gammopathy of renal significance is most helpful to indicate a causal relationship between the monoclonal gammopathy and the renal damage and because the significance of the monoclonal gammopathy is no longer undetermined. (*Blood*. 2012;120(22):4292-4295)

Introduction

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 < 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 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 smoldering multiple myeloma compared with 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 resulting from hypercalcemia or nonsteroidal anti-inflammatory drugs, 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.

Indeed, a growing number of pathologic renal conditions are being attributed to a clonal plasma cell disorder that 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. Because they do not meet conditions for smoldering multiple myeloma 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.” Despite their nonmalignant nature, these diseases are associated with a great deal of morbidity and even mortality.^{10,12,16} MGUS should not be used to describe hematologic disorders that result in kidney disease. It is because of 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

Table 1. Pathologic classification of diseases with tissue deposition or precipitation of monoclonal Ig

Organized	Nonorganized (granular)			
	Fibrillar	Microtubular	MIDD (Randall type)	Other
Myeloma cast nephropathy	Light chain amyloidosis	Type I and type II cryoglobulinemic glomerulonephritis	LCDD	Proliferative GN with monoclonal Ig deposits
Light chain proximal tubulopathy (with or without Fanconi syndrome)	Nonamyloid	Immunotactoid GN	LHCDD	Waldenström
Crystal-storing histiocytosis	Fibrillary GN*	GOMMID	HCDD	Macroglobulinemia

GN indicates glomerulonephritis; GOMMID, glomerulonephritis with organized microtubular monoclonal Ig deposits; LCDD, light-chain deposition disease; LHCDD, light and heavy-chain deposition disease; and HCDD, heavy-chain deposition disease.

*Mostly associated with polyclonal IgG deposits.

into animals.¹⁷ In addition, only 15% of AL amyloidosis and 65% of MIDD patients meet criteria for MM.^{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.¹⁸ In a large Italian study of MIDD patients, cytotoxic therapy was withheld from nearly 30% of those without MM.¹⁰ In those who were treated, none received vincristine-doxorubicin-dexamethasone or vincristine-doxorubicin-methylprednisolone, the standard therapy for MM at the time.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-year patient survival to be 89% and 70%, respectively, whereas the renal survival was only 67% and 37%, respectively.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 is characterized by monoclonal immunoglobulin deposits (most commonly IgG3κ) that results in a proliferative or membranoproliferative pattern of injury. These patients present with nephrotic range proteinuria and renal impairment.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.²¹ Recurrence of proliferative glomerulonephritis with monoclonal IgG deposits frequently occurs after kidney transplantation, which often results in rapid loss of the kidney allograft.²² So far, benefits of immunosuppression in proliferative glomerulonephritis with monoclonal IgG deposits 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.²³⁻²⁵ By immunofluorescence, these microtubules stain for immunoglobulins, most commonly IgG. A monoclonal protein can be detected in the majority of these patients. The histopathologic pattern is most similar to membranous or membranoproliferative glomerulonephritis (MPGN) or a mixture of the 2. Hematologically, 50% of patients have a lymphoma, most commonly chronic lymphocytic leukemia. The presence of MM in these patients is rare.²³⁻²⁵ Treating the underlying lymphoproliferative disorder generally leads to remission of proteinuria and stabilizing of renal function.²⁴ Immunotactoid glomerulopathy should not be confused with cryoglobulinemia, which also presents with large fibrils (30-50 nm) but are composed of cryoglobulins.²⁶ Of the 3 types of cryoglobulinemia, only types I and II are composed of monoclonal immunoglobulins. Type I is usually the result of a plasma cell dyscrasia, whereas 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 (Waldenström macroglobulinemia) can also result in kidney injury characterized by a mesangiocapillary glomerulonephritis.²⁷

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.^{28,29} However, a recent study of 68 MPGN patients, which excluded positive hepatitis (B and C) serology, dense deposit disease (type II MPGN) and those without a monoclonal protein study found that 41.1% had a monoclonal protein by serum and/or urine immunofixation.³⁰ 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 macroglobulinemia (1). Long-term follow-up of the patients with “MGUS” revealed 2 later progressed to MM and 1 to chronic lymphocytic leukemia.

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.³¹ The recurrence rate was 71.4% in these 7 patients versus 29.1% in patients without a detectable monoclonal gammopathy ($P = .14$). Although the small numbers failed to achieve statistical significance, this pattern is seen repeatedly in other MGRS kidney diseases.³¹⁻³³ In a single-center study, 5 of 7 (71.4%) patients with MIDD developed recurrence after kidney transplantation.¹¹ 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.³³ 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.³⁴ In contrast, 6 of the 10 allografts in (7) patients with monoclonal gammopathy had recurrence. Time to recurrence ranged from 3 to 87 months after transplantation.³⁰ 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.³⁵ Monoclonal protein studies should be performed to match the monoclonal protein in circulation with the monoclonal deposits in the kidney. Because 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.³⁶ Even when immunofixation is negative, an abnormal serum free light chain ratio can help identify the pathologic light chain involved in the kidney disease.³⁷ 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 exhibit 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 antiplasma cell therapies available. The fear of alkylator-induced myelodysplastic syndrome overshadowed the fear of ESRD.³⁸ With the advent of novel agents, this fear is much less warranted.³⁹ 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 > 5 years.⁴⁰⁻⁴⁵ Melphalan and dexamethasone have produced similar outcomes and may be more appropriate for high-risk patients.⁴⁶ Regimens containing novel agents, such as cyclophosphamide-thalidomide-dexamethasone, bortezomib-dexamethasone, cyclophosphamide-bortezomib-dexamethasone, and others, have also shown high response rates.⁴⁷⁻⁴⁹ 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.^{50,51} Similar strategies have also been found to be effective in patients with MIDD.⁵² Benefits in regard to the kidney have been demonstrated in patients with MIDD who achieved hematologic complete response (CR).⁵³⁻⁵⁵ Lymphoma-based regimens were found to be effective in 10 of 12 patients with fibrillary glomerulonephritis secondary to lymphoproliferative disorders.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 CR is the goal of therapy. First, evidence suggests that 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.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.⁵⁶ One recurrence actually occurred before definitive treatment. Both hematologic and kidney disease were controlled after a successful ASCT. Another ASCT-treated patient had a recurrence 52 months after kidney transplantation 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- versus double-ASCT, the relapse-free survival in MM after tandem ASCT was 36 months.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.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%.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 conclusion, MGRS-related kidney diseases are the result of toxic monoclonal protein produced by dangerous, small B-cell clones.¹² These disorders do not require treatment from a “tumoral” viewpoint (ie, 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 that result in renal damage. We think the term “monoclonal gammopathy of renal significance” 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: N.L., F.B., C.A.H., S.H.N., P.C., J.-P.F., A.D., K.W.S., and R.A.K. designed and wrote the manuscript.

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Correspondence: Nelson Leung, 200 First St SW, Rochester, MN 55905; e-mail: leung.nelson@mayo.edu.

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