Paraprotein–Related Kidney Disease: Diagnosing and Treating Monoclonal Gammopathy of Renal Significance


Abstract
Paraprotein–related kidney disease represents a complex group of diseases caused by an abnormal paraprotein secreted by a clone of B cells. The disease manifestations range from tubulopathies, such as the Fanconi syndrome, to a spectrum of glomerular diseases that can present with varying degrees of proteinuria and renal dysfunction. Diagnosis of these diseases can be challenging because of the wide range of manifestations as well as the relatively common finding of a serum paraprotein, especially in elderly patients. Thus, renal biopsy along with detailed hematologic workup is essential to link the presence of the paraprotein to the associated renal disease. Recent advances in treatment with more effective and targeted chemotherapies, as well as stem cell transplantation, have improved the renal and overall prognosis for many of these disorders.

Introduction
Paraproteins are monoclonal Igs (or their components) produced by clones of the B cell lineage. Monoclonal gammopathy (MG) occurs in all five Ig isotypes (A, G, M, D, and E). IgG, the most abundant Ig, makes up the majority of MG, whereas IgE is the rarest (1–3). Ig light chain only MG also exists and is present in 0.7%–0.8% of the population above the age of 45 years old (4,5). All five isotypes can be produced by plasma cells, but less differentiated B cells are more limited in the isotypes that they can produce. Clones with lymphoplasmacytic differentiation (Waldenström) nearly always produce IgM, whereas CD5+ CD23+ lymphocytes (chronic lymphocytic leukemia [CLL]) are more likely to produce IgG and rarely, IgA (6,7).

MG is a biomarker of the clonal proliferation of cells producing the monoclonal Ig. For plasma cells, this represents a spectrum from monoclonal gammopathy of undetermined significance (MGUS), a benign condition by definition, to the malignant condition multiple myeloma (MM) characterized by either the impending or presence of end organ damage (8). Monoclonal B cell lymphocytosis represents the MGUS-like stage in CLL, and smoldering Waldenström macroglobulinemia (WM) is the lymphoplasmacytic lymphoma that has yet to progress to clinically important WM (9,10). Disease progression is typically signified by a rise of the monoclonal protein measured by a monoclonal spike or serum free light–chain (sFLC) concentration (11,12).

In addition to being a biomarker, paraproteins can also be nephrotoxic. The two most common scenarios are during progression to MM or WM. As the concentration of sFLC rises, the risk of cast formation resulting in light–chain cast nephropathy (LCCN) also increases, which is a myeloma-defining event (8). The second scenario is hyperviscosity syndrome caused by the high levels of monoclonal protein most commonly observed in WM, but they can occur in MM (9). These disease-defining events signify a tumor burden sufficient to cause organ damage. However, the paraprotein can play a direct role in the pathogenesis of kidney disease independent of its concentration or tumor burden. In these conditions, the progression of the clone is not required. In fact, the clonal characteristics are much more similar to MGUS, smoldering WM, and monoclonal B cell lymphocytosis than their malignant counterparts. The term monoclonal gammopathy of renal significance (MGRS) was introduced by the International Kidney and Monoclonal Gammopathy Research Group to separate these entities from both the benign and the malignant hematologic conditions (13).

MGRS represents all B cell lymphoproliferative and plasma cell proliferative disorders that do not meet criteria for MM, WM, CLL, or malignant lymphoma but are associated with a kidney disease resulting from a paraprotein (13). By this definition, LCCN is not an MGRS renal lesion, because it is almost always secondary to MM. There are two important characteristics to recognize regarding these lesions. First, LCCN and the other MGRS renal lesions are determined by the MG. Thus, they can be seen in plasma cell clones as well as WM or CLL. Second, aside from LCCN, the other lesions are more commonly seen in nonmalignant state (MGRS) than in MM, WM, and CLL. These independent nephrotoxic properties of paraproteins have been shown in animal studies (14). In humans,
this can be seen in Ig light-chain (AL) amyloidosis, where 40% of patients have >10% bone marrow plasma cells, but <20% meet criteria for MM (15). Similarly, 59% of patients with monoclonal Ig deposition disease (MIDD) in one study were labeled as having myeloma, but two recent studies that used the hypercalcemia, renal impairment, anemia, and bone lesions criteria found that only 20% of patients met the definition for MM (16–18). Before MGRS, these conditions were not designated as clonal disorders, and myeloma (lymphoma) therapies were withheld, resulting in poor response and progression of kidney disease (18–20). The proper classification of these diseases not only improved our understanding but will help design future treatment strategies (21,22).

Renal Lesions Associated with MGRS

Many kidney diseases are related to the deposition or precipitation of monoclonal Ig. These lesions are common in patients with paraproteinemia and associated with high morbidity and mortality. As discussed later, the clinical manifestations, histologic findings, involvement of other tissues, and prognosis of MGRS renal lesions are variable. Many of these manifestations are possibly determined by the nature and the rate of production of the pathogenic monoclonal Ig as well as the local microenvironment (23,24).

Monoclonal Ig light–chain deposition is observed in most patients, whereas the deposition of the whole Ig is less common, and monoclonal heavy–chain deposition is rarest of all. The deposition of monoclonal Ig can occur in the glomeruli, tubulointerstitium, and vasculature. MGRS renal lesions are usually classified by the localization and the types of the deposit (21,22,25,26). Glomerular capillaries and the mesangium are the favorable sites of monoclonal Ig deposition (26). Those with glomerular lesions are divided into two categories on the basis of the ultrastructural characteristics of their deposits. Glomerular diseases with organized deposits include AL amyloidosis, types 1 and 2 cryoglobulinemic GN, and immunotactoid GN (also known as GN with organized microtubular Ig deposits). Glomerular diseases with nonorganized deposits include MIDD, proliferative GN with monoclonal Ig deposits (PGNMID), and C3GN with MG.

MGRS, plasma cell, and lymphocytic neoplasms can also produce tubulointerstitial disease that includes light–chain proximal tubulopathy (LCPT) with or without Fanconi syndrome and LCCN (21). Free light chains (FLCs) filtered through the glomerulus are normally reabsorbed by proximal tubules and degraded by the lysosomal degradation system. However, the production of pathologic amounts of FLCs can exceed the reabsorptive capacity of proximal tubules, resulting in the excess of FLCs in the distal tubules, resulting in the excess of FLCs in the distal tubules, as shown in ultrastructural studies (28). Often, electrolyte wasting and aminoaciduria occur, which are characteristic of Fanconi syndrome. More than one type of deposit from the same monoclonal Ig can coexist in the same patient (29).

In the vascular compartment, deposits can be in the form of amyloid fibrils and crystals. Approximately 5% of patients with AL amyloidosis will have predominately vascular deposition of amyloid without significant glomerular deposition (30). These patients present with progressive renal insufficiency without significant proteinuria. Crystalglobulinemia and cryocrystalglobulinemia are rare types of MGUS renal lesions. They usually cause peripheral arterial thrombosis, resulting in limb ischemia, but in severe cases, visceral organs, including the kidney, can become involved (31). They differ from crystal storage histiocytosis, in which the crystals are intracellular instead of intravascular. Vascular involvement is also seen in cryoglobulinemia with vasculitis and intracapillary thrombi (32).

MGRS renal lesions can also mimic renal diseases typically caused by polyclonal Igs. A type of membranous nephropathy has been described secondary to a monoclonal Igκ targeting the phospholipase A2 receptor (33). Recurrent pulmonary renal syndrome caused by antiglomerular basement membrane disease secondary to a monoclonal IgAlκ has also been reported (34). Finally, in general, nonamyloid fibrillary GN is not typically considered to be MGRS related, because the deposits are usually polyclonal IgG and not accompanied by clonal B cell proliferative disorder. However, 17% of 66 patients in one study were found to have an MG, making a thorough MG testing important in these patients (21,35).

Clinical Characteristics of MGRS Renal Disease

The spectrum of MGRS renal lesions varies widely, with pathology affecting different portions of the nephron. Disorders associated with MGRS have been reported to present in middle-aged to older patients, with the majority of patients presenting at >50 years of age (17,20,36). Sex predominance seems to be variable depending on the specific disorder, with MIDD and amyloidosis reported as more common in men, whereas a cohort of patients with PGNMID reported a preponderance of women (17,20,37).

MGRS–related glomerular disorders are associated with chronic deterioration of renal function, with a proportion of patients progressing to end stage disease. Proteinuria can range from subnephrotic to nephrotic range, with some patients presenting with overt nephrotic syndrome. Hematuria is usually microscopic in nature, and systemic hypertension is often present (17,20,21,36). Type 1 cryoglobulinemic GN may also be associated with acute deterioration of renal function with a nephritic-type picture (Table 1) (21,38). Amyloidosis is less likely to be associated with hematuria and hypertension and strongly associated with nephrotic-range proteinuria (21,37,39). Extrarenal manifestations are common in AL amyloidosis, type 1 cryoglobulinemic GN, and MIDD, affecting the heart, liver, lung, skin, joints, and peripheral nerves to various degrees (21,38,39).

Tubular disorders (Table 1) may present with varying degrees of progressive CKD, tubular proteinuria, and proximal tubular dysfunction (glycosuria, phosphaturia, and type 1 renal tubular acidosis) (21). Extrarenal manifestations, such as osteomalacia, may be associated with Fanconi syndrome related to urine phosphate wasting (40). The bone marrow, liver, spleen, lymph nodes, lung, skin, and cornea may be affected in crystal-storing histiocytosis (21).
Table 1. Characteristic histopathologic features of monoclonal gammopathy of renal significance–related disorders on renal biopsy

<table>
<thead>
<tr>
<th>Glomerular Disorders</th>
<th>Pathology Findings</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>PGNIM (3)</strong></td>
<td>Membranoproliferative GN, diffuse and global double–contoured glomerular capillary walls with mesangial expansion</td>
</tr>
<tr>
<td><em>Light</em></td>
<td>Glomerular granular deposits of monoclonal light chains</td>
</tr>
<tr>
<td><em>IF</em></td>
<td>Most commonly, subendothelial electron–dense deposits; less commonly, subepithelial deposits</td>
</tr>
<tr>
<td><em>EM</em></td>
<td>Global nodular mesangial sclerosis, PAS positive; may be corresponding TBM thickening</td>
</tr>
<tr>
<td><strong>MIDD (1)</strong></td>
<td>Diffuse linear monoclonal protein deposition along GBMs and TBMs (light chain only for LCDD, light and heavy chain for LHCDD, and single class of Ig in HCDD)</td>
</tr>
<tr>
<td><em>Light</em></td>
<td>Presence of punctate, powdery electron–dense deposits along GBMs and TBMs</td>
</tr>
<tr>
<td><em>IF</em></td>
<td>Membranous or membranoproliferative GN pattern; Congo red negative</td>
</tr>
<tr>
<td><em>EM</em></td>
<td>Glomerular deposits with light-chain restriction; may also stain for IgG (most commonly IgG1) and C3</td>
</tr>
<tr>
<td><strong>ITGN (2,5)</strong></td>
<td>Subepithelial or subendothelial electron–dense deposits with parallel arranged microtubules and hollow cores; usually &gt;30 nm in diameter</td>
</tr>
<tr>
<td><em>Light</em></td>
<td>Membranoproliferative GN pattern, less likely diffuse proliferative GN; Congo red negative</td>
</tr>
<tr>
<td><em>IF</em></td>
<td>Most commonly polyclonal deposits of Ig, typically IgG</td>
</tr>
<tr>
<td><em>EM</em></td>
<td>Randomly oriented nonbranching fibrils; 12–24 nm in diameter</td>
</tr>
<tr>
<td><strong>FGN (2,5)</strong></td>
<td>Amorphous/acellular mesangial expansion, weakly PAS positive, silver negative, Congo red positive</td>
</tr>
<tr>
<td><em>Light</em></td>
<td>Intense staining for single light chain for AL amyloidosis (&gt;75% expressing A), intense staining for single Ig heavy chain (most commonly γ) with negative light chains for AH amyloidosis, intense staining for single heavy Ig chain and single light chain for AHL amyloidosis</td>
</tr>
<tr>
<td><em>IF</em></td>
<td>Randomly oriented nonbranching fibrils; 8–12 nm in diameter</td>
</tr>
<tr>
<td><strong>Amyloidosis (4,5,7)</strong></td>
<td>Predominantly membranoproliferative or endocapillary proliferative GN; likely large strongly eosinophilic glassy intraluminal deposits</td>
</tr>
<tr>
<td><em>Light</em></td>
<td>Monoclonal light and heavy chains (most commonly IgGκ) and complement</td>
</tr>
<tr>
<td><em>IF</em></td>
<td>Glomerular capillary lumina segmentally occluded by large electron–dense subendothelial and intracapillary deposits; may appear organized in over one half of patients</td>
</tr>
<tr>
<td><strong>C3 glomerulopathy with monoclonal gammopathy (5)</strong></td>
<td>Membranoproliferative GN; mesangial proliferation; may be endocapillary proliferative pattern</td>
</tr>
<tr>
<td><em>Light</em></td>
<td>C3+ C1q deposits with granular C3 deposits in mesangium and capillary walls; paucity or absence of Ig deposits</td>
</tr>
<tr>
<td><em>IF</em></td>
<td>Sausage–shaped intramembranous and large rounded mesangial electron–dense deposits in DDD; ill–defined mesangial, intramembranous, and subendothelial deposits in C3GN</td>
</tr>
<tr>
<td><strong>Tubular disorders</strong></td>
<td>PTC atrophy and dedifferentiation, intracytoplasmic inclusions</td>
</tr>
<tr>
<td><strong>Fanconi syndrome (5)</strong></td>
<td>PTC light–chain inclusions, most commonly κ</td>
</tr>
<tr>
<td><em>Light</em></td>
<td>Rhomboid crystals within PTC lysosomes or free in the cytoplasm</td>
</tr>
</tbody>
</table>
Table 1. (Continued)

<table>
<thead>
<tr>
<th>Glomerular Disorders</th>
<th>Pathology Findings</th>
</tr>
</thead>
<tbody>
<tr>
<td>Proximal light-chain tubulopathy (5)</td>
<td>PTC atrophy and dedifferentiation, PTC cytoplasmic swelling</td>
</tr>
<tr>
<td>Light IF EM</td>
<td>PTC light-chain staining, A or ( \kappa )</td>
</tr>
<tr>
<td></td>
<td>Amorphous granules accumulations of light chains; increased lysosomes with mottled appearance</td>
</tr>
<tr>
<td>Crystal-storing histiocytes (5)</td>
<td>Histiocytes with crystalline inclusions in interstitium and perirenal fat; PTC atrophy and dedifferentiation</td>
</tr>
<tr>
<td>Light IF EM</td>
<td>PTC light-chain inclusions, most commonly ( \kappa )</td>
</tr>
<tr>
<td></td>
<td>Needle-shaped crystals within histiocytes and occasionally, in PTC and glomerular cells</td>
</tr>
</tbody>
</table>

PGNMID, proliferative GN with monoclonal Ig deposits; IF, immunofluorescence; EM, electron microscopy; MIDD, monoclonal Ig deposition disease; PAS, periodic acid–Schiff; TBM, tubular basement membrane; GBM, glomerular basement membrane; LCDD, light-chain deposition disease; LHCDD, light- and heavy-chain deposition disease; HCDD, heavy-chain deposition disease; ITGN, immunotactoid GN; FGN, fibrillary GN; AL amyloidosis, light-chain amyloidosis; AH amyloidosis, heavy-chain amyloidosis; AHL amyloidosis, heavy-/light-chain amyloidosis; DDD, dense deposit disease; PTC, proximal tubular cell.
link between the MG and type of nephropathy. With the recent discovery of masked antigens, antigens retrieval by paraffin immunofluorescence after protease digestion should occur in all patients with C3GN (52,53). Screening for the presence of a monoclonal Ig should begin with serum and urine protein electrophoresis. This should be combined with serum and urine immunofixation, which allows for identification of the Ig isotype and increases the sensitivity in detecting a monoclonal Ig (21,54,55). It should be stressed that both serum and urine studies should be performed as the diagnostic sensitivity, especially in patients with AL amyloidosis or a small B cell clone, is increased by this strategy (56). To further maximize the sensitivity of the diagnostic workup, these serum and urine studies should be supplemented with the sFLC assay (57). The FLC assay is useful in suggesting clonality when the serum ratio of $\kappa$ to $\lambda$ is abnormal (58). However, because of the important role of the kidney in clearance of FLCs, patients with abnormal GFRs may have a shift in the normal range of the FLC ratio, and it is recommended that an FLC ratio of 0.37–3.17 be used instead of the values in those with normal kidney function (0.26–1.65) (59,60).

After the finding of an MG, the search for the underlying B cell clone should include a bone marrow aspirate and biopsy that is often supplemented with flow cytometry and immunohistochemistry studies. In those patients with an IgM monoclonal Ig or a high suspicion for lymphoma, a search for pathologic lymph nodes may be required, because these patients may have a nonplasmacytic B cell clone that can be only found with lymph node biopsy (21).

**Treatment Principles of MGRS**

Because MGRS is produced by B cell clones, the treatment of MGRS renal disease is generally aimed at eradication of the monoclonal Ig producing malignant clone rather than the renal lesion itself. Although these clones in general represent low malignancy burden, treatment is indicated to preserve renal function or in patients with advanced CKD leading to kidney transplant, prevent the recurrence in the allograft (13).

One of the most devastating and common complications of monoclonal Ig affecting the kidneys is AL amyloidosis. Because patients with AL amyloidosis often have cardiac involvement and because cardiac disease is the major determinate of mortality, it is important to evaluate patients for evidence of cardiac amyloid (22). Patients who meet the selection criteria are offered ASCT as a treatment option, because it offers a superior survival benefit when performed in properly selected patients (61). Unfortunately, only 20% of the patients meet eligibility criteria. Patients who are ineligible for ASCT can undergo cytotoxic therapy on the basis of the combination of melphalan or cyclophosphamide in patients with more advanced CKD augmented by bortezomib and dexamethasone (62–64). Renal outcomes in patients with renal amyloidosis treated with chemotherapy were evaluated in a large retrospective cohort. Of the 429 patients, 32.6% showed renal response with decreased proteinuria and <25% increase in serum creatinine. Renal response was strongly correlated with a >90% reduction in FLC (65). In the same group, 21 patients underwent renal transplantation. The 5-year patient survival rate was 71.4%, and there were no graft failures caused by recurrent amyloid; however, two patients died from progressive extrarenal amyloidosis (47).

MIDD, which in most patients, is caused by $\kappa$-light chain light–chain deposition disease, is associated with a high risk for ESRD (17). In the largest series of 56 patients with MIDD who were followed for a median of 25 months, eight patients were not treated, and five (63%) of them...
progressed to ESRD. Thirty-two patients were treated with chemotherapy, and 11 (34%) progressed to ESRD, whereas 16 underwent ASCT, with six (38%) progressing to ESRD in this subgroup. A recent study showed that bortezomib-based therapy achieved an overall hematologic response rate of 91%, with 70.4% being very good partial response (VGPR) or better. In this study, patients who achieved a VGPR or better were more likely to experience a renal response versus those who did not (71% versus 22%; P = 0.001) (16). Another study also found bortezomib-based therapy to be highly effective, achieving a complete response in 89% of patients, whereas other agents, including thalidomide-, lenalidomide-, and alkylator-based therapies, were not as effective (66). However, 81% of patients who underwent consolidation therapy with high-dose melphalan followed by ASCT achieved a complete response, with only 5% risk of treatment-related mortality. Better renal outcome was seen in patients with VGPR or better and those with baseline CKD stage 3 or less. Improved outcomes after ASCT were reported by another group, with six of seven patients showing improved or stable renal function with median follow-up of 23.6 months (45). A panel of experts recommends that MIDD treatment should be on the basis of the CKD stage at presentation (22). For CKD stages 1–3, the main goal of treatment is preservation of renal function, and initial therapy should include bortezomib-based therapy followed by high-dose melphalan with ASCT in appropriately selected patients with no extrarenal manifestations. In patients ineligible for ASCT, bortezomib-based regimen alone can be considered, because it has been shown to improve renal outcomes, particularly in patients with pretreatment GFR >30 ml/min per 1.73 m³ and post-treatment dFLC (difference between involved and uninvolved FLC) <40 mg/L (16). In CKD stages 4 and 5, the probability of renal recovery is low, and treatment is not recommended unless there is extrarenal involvement or renal transplantation is planned. However, it should be noted that the recurrence rate in patients undergoing kidney transplantation is high, and complete hematologic response is essential before transplantation is considered (16,17,41).

Acquired Fanconi syndrome or LCPT results from crystalline or noncrystalline cytoplasmic deposits of predominantκ-light chain (21,53). Aside from the metabolic complications discussed previously, this syndrome is fairly benign with slow progression to ESRD, with most patients dying from other causes (67). Only one of 14 patients with MGUS and acquired Fanconi syndrome progressed to MM in one case series. Treatment did not have significant effects on the renal function in these patients. Because of the indolent nature of this condition, these authors felt that treatment should be supportive, with electrolyte supplementation to prevent osteomalacia (67). It is important to note that patients from this series were treated with alkylator-based therapies, which resulted in 19% of deaths caused by alkylator–related secondary leukemia and myelodysplastic syndrome. A more recent study of patients treated predominately with novel agents (bortezomib, thalidomide, and lenalidomide) and stem cell transplantation found improvement of renal function in 31.8% and stabilization in another 50% versus 14.2% improvement and 57.1% stabilization in untreated patients (68). ESRD was only reported in the untreated patients and occurred in 28.5% of patients. Death occurred in 33.3% of patients treated with chemotherapy alone and 37.5% of untreated patients. The only independent predictor of the final renal function was the initial renal function, indicating the importance of early detection. The safety of the novel agents and stem cell transplant made it practical to preserve renal function in those with mild CKD. However, the risk may outweigh the benefits in patients with advanced CKD who are ineligible for kidney transplantation and do not have MM (22).

Treatments of other less common renal disorders associated with MGRS, such as membranoproliferative glomerulonephritis, immunotactoid GN, and PGNMID, are all aimed at eradication of malignant clone. The chemotherapy choice is on the basis of whether the clone is believed to be of lymphocytic or plasmacytic origin (22).

Conclusions
Paraprotein–related kidney disease represents a wide range of kidney diseases that are the results of MGRS or MM/WM. Although the presentation and histology are diverse, their progressive nature and tendency to recur after kidney transplantation are common. A kidney biopsy is required for diagnosis, and establishment of the pathogenesis of the monoclonal protein is required before cytotoxic treatment. Treatment should target the pathologic clone responsible for the production of the nephrotoxic MG.

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