Reducing Diagnostic Errors — Recognizing Monoclonal Gammopathy of Renal Significance (MGRS)

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ABSTRACT

Recently, the term monoclonal gammopathy of renal significance (MGRS) was used to describe monoclonal gammopathies capable of causing kidney damage resulting in chronic kidney impairment and end-stage renal disease. By definition, patients with MGRS have small plasma-cell or B-cell clones that do not meet the criteria for multiple myeloma or lymphoma, and are frequently mistaken as monoclonal gammopathies of undetermined significance (MGUS). As treatment is not recommended for MGUS, appropriate therapy is commonly withheld. Therefore, a high index of clinical suspicion for MGRS and a multidisciplinary approach are essential to avoid delayed diagnosis and the development of MGRS-related end-stage renal disease.

INTRODUCTION

There are several possible mechanisms by which a plasma-cell clone may cause renal impairment. The prototype renal disorder associated with a plasma-cell neoplasm is myeloma cast nephropathy in which a high disease burden leads to overproduction of light chains and formation of casts that obstruct renal tubules.1,2

Unlike multiple myeloma (MM), there are several other ways by which a monoclonal gammopathy produced even from a small plasma-cell clone may lead to renal impairment. In these cases, the production of nephrotoxic monoclonal proteins is responsible for the renal damage. From a hematological perspective, such cases may be mistakenly diagnosed as monoclonal gammopathy of undetermined significance (MGUS).3 Therefore, the term “monoclonal gammopathy of renal significance” (MGRS) was introduced in 2012 by the International Kidney and Monoclonal Gammopathy Research Group to differentiate MGUS from monoclonal gammopathies associated with renal dysfunction. The group of MGRS is heterogenous, including several different histological entities.4

Our aim in this article is to provide a contemporary summary of the classification of MGRS and discuss various diagnostic challenges faced by clinicians when consulting patients with suspected MGRS.

KEYWORDS: Amyloidosis, light chain deposition disease, fibrillary glomerulonephritis, immunotactoid glomerulonephritis, cryoglobulinemic glomerulonephritis, C3 nephropathy
**Types of Plasma-cell Disorders**

Knowledge of the different types of plasma-cell disorders is central to understanding the concept of MGRS. We will start this article with a brief description of the classification criteria for the various types of plasma-cell disorders.

Monoclonal plasma-cell disorders include MGUS, smoldering myeloma (SMM), and MM. These disorders are differentiated on the basis of well-defined criteria. MM is characterized by ≥10% clonal bone-marrow plasma cells and evidence of end-organ damage — i.e., hypercalcemia, renal insufficiency, anemia, and lytic bone lesions (CRAB criteria). In 2014, the diagnostic criteria were updated by adding biomarkers that can identify patients who will develop end-organ damage. These criteria, so-called “myeloma defining events” (MDE), include ≥60% clonal bone-marrow plasma cells, involved-to-uninvolved free-light-chain ratio ≥100, and ≥2 focal lesions (≥25 mm) on MRI.

Smoldering multiple myeloma (SMM) is defined by a serum monoclonal protein ≥30 g/l, clonal bone-marrow plasma cells ≥10%, and absence of CRAB/MDE. MGUS is defined by serum paraprotein <30 g/l, bone-marrow plasma cells <10%, and absence of CRAB. MGUS is common in people over 50 years with an incidence of 3.5% and 5% for those <10%, and absence of CRAB. MGUS is defined by serum paraprotein <30 g/l, clonal bone-marrow plasma cells <10%, and absence of CRAB. MGUS is common in people over 50 years with an incidence of 3.5% and 5% for those over 70 years.

The hematological features of MGRS are frequently compatible with MGUS. By contrast to MGUS, MGRS are rare conditions. In MGRS, a monoclonal protein produced from a plasma-cell clone is directly linked to renal damage.

**When Should MGRS be Suspected?**

A high index of suspicion for MGRS should be maintained in patients with renal impairment in whom a monoclonal paraprotein is found in serum or urine or have evidence of a monoclonal plasma-cell disorder in the bone marrow. Diagnosis of MGRS relies on renal histology to demonstrate pathological evidence of paraprotein-induced renal damage and exclude cast nephropathy as well as other causes of renal disease such as diabetes and hypertension. As seen in the following examples, patients can present to either a nephrologist or hematologist.

**Case 1**

A 68-year-old man was admitted to our Nephrology Department with proteinuria and deterioration of renal function (creatinine 1.8 mg/dl) on routine annual tests. His history was unremarkable except for mild hypertension treated with amlodipine. He had not taken nephrotoxic drugs. Renal ultrasound showed no abnormalities. Further evaluation showed mild normocytic anemia, 24-hour urine protein 1.7 g, and ANA 1:160 with normal C3, C4, and RF. Hepatitis B and C were negative. Serum protein electrophoresis was negative with normal immunoglobulin levels. Urine electrophoresis was negative, however, urine immunofixation revealed a small kappa-free monoclonal component. MGRS was suspected and kidney biopsy showed findings consistent with light-chain deposition disease. On hematological evaluation, bone-marrow biopsy showed 5% kappa-restricted monoclonal plasma cells consistent with MGUS. The patient was treated with chemotherapy with improvement in renal parameters.

**Case 2**

A 60-year-old woman with a history of IgG kappa MGUS was examined during a routine follow-up. She reported having elevated blood pressure and discoloration of her fingers after exposure to cold in the last month. There was no change in the paraprotein level, as compared to previous examinations. Urinalysis showed protein 1+, 10-12 erythrocytes/hpf, and occasional casts. Laboratory tests revealed creatinine 2.1 mg/dl and mild proteinuria (400 mg/24h). She was referred to a nephrologist. Testing for ANA, C3, C4, RF, hepatitis B and C was negative. Kidney biopsy showed evidence of cryoglobulinemic glomerulonephritis with monoclonal kappa light-chain staining. Trace cryoglobulin was found in serum (cryocrit <0.5%).

The patient was referred to the Hematology Department for management of type I cryoglobulinemia.

**Diagnostic Approach in Suspected MGRS**

**Hematological Evaluation**

Hematological evaluation includes serum and urine protein electrophoresis combined with immunofixation (IFX) and serum free light-chain (FLC) analysis.

Serum protein electrophoresis (SPEP) can detect a paraprotein when its concentration is ≥0.5 g/l. IFX is more sensitive, able to detect monoclonal proteins ≥0.15 g/l. Knowing these limitations is important because the concentration of monoclonal protein in some cases of MGRS may be below threshold. Plasma cells may produce intact immunoglobulin or light chain alone. Light chains are rapidly excreted and concentrated in urine, therefore, serum electrophoretic assays often fail to identify monoclonal light chains. Urine protein electrophoresis and immunofixation from a 24-hour urine collection can detect urinary light chains at a concentration of >0.01 mg/l. The serum free light-chain (FLC) assay measures free-kappa and free-lambda light chain with increased sensitivity using a nephelometric immunoassay. The normal range of the free kappa-to-lambda ratio is 0.26-1.65 with normal renal function, and 0.37-3.17 in renal impairment.

Bone-marrow aspiration and biopsy with immunohistochemical analysis should be performed in suspected MGRS.
to evaluate the underlying plasma-cell dyscrasia (or B-cell clone). Usually, bone marrow aspiration and trephine biopsy are reported to show only a small increase in the percentage of plasma cells or to be normal. Flow cytometry should be undertaken to establish clonality whenever small numbers of plasma cells are present as monoclonal plasma cells are detectable in 97% of patients by immunophenotyping. Bone-marrow cytogenetics and fluorescent in situ hybridization (FISH) analysis may provide useful additional information.9,10

Nephrological Evaluation

Patients may present with diverse clinical manifestations depending on the underlying renal lesions such as acute kidney injury (AKI), selective or non-selective proteinuria, acute glomerulonephritis/nephritic syndrome, Fanconi’s syndrome, and microscopic hematuria, reflecting the heterogeneity of the pathologic features in patients with MGRS. The type of renal injury depends on the molecular and physicochemical properties of the monoclonal protein and not its “burden” as in cast nephropathy. Kidney biopsy is indicated in all patients with suspected MGRS to assess the type of renal injury, severity of renal damage, impact on renal function, generation of fibrous tissue, and renal prognosis. Specimens should be examined with light microscopy (LM), immunohistochemistry (IHC), immunofluorescence (IF), and electron microscopy (EM). Importantly, since diagnosis is often based on subtle morphological changes, evaluation by an expert renal pathologist should be sought for a definite diagnosis.

Classification of MGRS

MGRS are classified anatomically, taking into account the position of the primary renal lesion caused by the deposition of the monoclonal protein and its clinical sequelae (Table 1). However, LM and IF are not always capable to determine the nature of the monoclonal deposits. EM is particularly valuable for this purpose, and a more accurate classification of MGRS is based on the ultrastructural appearance and pattern of the monoclonal immunoglobulin deposits (organized deposits versus non-organized deposits) (Fig. 1). Organized deposits occur extracellularly in various forms (fibrils, microtubules,

### TABLE 1. Primary renal lesions and clinical manifestations.

<table>
<thead>
<tr>
<th>DISEASE</th>
<th>Glomerulus</th>
<th>Tubular</th>
<th>Proteinuria</th>
<th>GFR</th>
<th>Hematuria</th>
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<td>LCDD</td>
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<td>C3 GN</td>
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<td>PGNMID</td>
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GN: denotes glomerulonephritis; LCDD: denotes light-chain deposition disease; PGNMID: denotes proliferative glomerulonephritis with monoclonal IgG deposits.

![Diagram of MGRS based on the deposits. GN: denotes glomerulonephritis; LCDD: denotes light-chain deposition disease; PGNMID: denotes proliferative glomerulonephritis with monoclonal IgG deposits.](image-url)
curved microtubules, crystals and fingerprints), diameters, and localizations. Non-organized deposits usually have a microgranular appearance which is also seen with IF microscope.\textsuperscript{11}

**MGRS WITH ORGANIZED DEPOSITS**

**1. IMMUNOGLOBULIN LIGHT-CHAIN (AL) AND HEAVY-CHAIN (AH) AMYLOIDOSIS**

Amyloidosis is a general term for diseases of protein folding in which a precursor protein aggregates and forms insoluble amyloid fibrils deposited extracellularly in tissues.\textsuperscript{12, 13} Monoclonal immunoglobulin light chain and heavy chain are responsible for AL and AH amyloidosis, respectively. AH amyloidosis is extremely rare. In AL amyloidosis, the fibrils are formed by a fragment of a monoclonal light chain; lambda light chains are more commonly associated with amyloid than kappa in approximately a 3:1 ratio. Typically, the amyloidogenic clone is small (bone-marrow plasma-cell count 5-10\%).\textsuperscript{14} Kidney, heart, liver, and peripheral nerves may be affected. 60\% of patients are between 50 and 70 years old at diagnosis and only 10\% are aged under 50 years.

Using LM, renal amyloid appears as amorphous material occurring mainly in the mesangium and basement membranes of the glomerulus. Amyloid may also be found in the tubulointerstitium and in the vessel walls. Characteristically, the lesions stain positive with Congo red, producing a classical apple green birefringence under polarized light (Fig. 2). Silver stains are negative and PAS stain is usually weakly positive. IF reveals a single light-chain isotype, usually lambda. On EM, amyloid contains randomly arrayed fibrils 8-15 nm in diameter.\textsuperscript{15, 16}

From a clinical perspective, AL amyloidosis is a disease with insidious onset. Although AL amyloid deposits generally affect multiple organs, dysfunction of one particular organ often predominates. Nearly one half of patients have dominant renal amyloid at diagnosis which is predominantly a glomerular lesion characterized by substantial proteinuria (>0.5 g/24 hours). Albumin is the main urinary protein consistent with the nephrotic syndrome. Symptoms include ankle swelling, fatigue, loss of energy, peripheral edema, pleural effusions, and occult pericardial effusions. Loss of renal excretory function is common in AL amyloidosis although presentation with progressive renal failure at diagnosis is rare. Extensive deposits in the interstitium and vessels are characteristically accompanied by a decline in GFR. Less common features include arterial hypertension, nephrogenic diabetes insipidus, and Fanconi’s syndrome owing to amyloid deposits in the vasculature, collecting duct, and proximal tubules, respectively. Notably, there is poor correlation between the extent of amyloid deposits and severity of clinical findings.\textsuperscript{15, 17, 18}

**2. CRYOGLOBULINEMIC GLOMERULONEPHRITIS**

Cryoglobulins are serum immunoglobulins that precipitate below 37°C and dissolve upon rewarming. Cryoglobulinemia has been described in various illnesses, including hepatitis C, lymphoproliferative disorders, systemic lupus erythematosus, rheumatoid arthritis, and cryoglobulinemic glomerulonephritis.

**FIGURE 2.** Renal AL amyloidosis. Congo red stain showing amyloid deposits in mesangium, vessels and tubules (arrows in left panel), that demonstrate typical apple green birefringence with polarized light (right panel). (from K. Liapis: personal archive).
Cryoglobulinemia is classified on the basis of the clonality and type of immunoglobulin. Type I cryoglobulinemia consists of monoclonal immunoglobulin (IgM, IgG, or IgA) cryoglobulins. Type II cryoglobulinemia consists of a mixture of monoclonal IgM and polyclonal IgG cryoglobulins. Type III cryoglobulinemia consists of a mixture of two or more immunoglobulin isotypes without a monoclonal component. Cryoglobulin types I and II may be seen in association with a monoclonal plasma-cell or B-cell disorder. Cryoglobulinemia is complicated by cryoglobulinemic glomerulonephritis (membranoproliferative glomerulonephritis) in 25%, which may present with the clinical picture of nephritic syndrome, nephrotic syndrome, hypertension, subnephrotic proteinuria, hematuria, and AKI.

Using LM, cryoglobulinemic glomerulonephritis shows features of membranoproliferative or proliferative glomerulonephritis with hyaline thrombi within capillaries (Fig. 3). Silver staining shows segmental duplication of capillary walls and mesangial expansion and proliferation. IF shows staining of capillary thrombi that are monoclonal for light chain (more frequently kappa than lambda kappa in approximately a 3:1 ratio). When viewed with EM, cryoglobulin deposits are found in the glomeruli, mainly in the subendothelial wall and inside the capillary lumen leading to capillary obstruction. Specific appearances of the subendothelial deposits have been described including fibrillar, microtubular, and fingerprint forms.

3. FIBRILLARY GLOMERULONEPHRITIS (FG)

FG is a rare disorder, seen in less than 1% of renal biopsy specimens. Clinically, patients may present with various degrees of renal insufficiency, nephrotic-range proteinuria, hypertension, and microhematuria. FG is a difficult diagnosis that requires considerable expertise and use of EM. Histologically, it is characterized by mesangial hypercellularity, duplication of the glomerular basement membranes, and glomerular deposits of Congo-red negative fibrillary material. These fibrils usually stain with IgG and C3 immunostains. By contrast to amyloid fibrils, FG shows randomly arranged fibrils that are 16 to 24 nm in diameter (Fig. 4). Only a minority of FG cases are associated with monotypic glomerular deposits, as seen on IF and IHC studies, and therefore, should be considered consistent with MGRS.

4. IMMUNOTACTOID GLOMERULONEPHRITIS (IG)

IG is an uncommon entity characterized by microtubular monoclonal immunoglobulin deposits in the glomeruli. To make a diagnosis, cryoglobulinemic glomerulonephritis and lupus nephritis should be ruled out. LM findings in cases of IG are non-specific, including Congo-red negative and silver-stain negative mesangial deposits of amorphous material accompanied by membranous or membranoproliferative pattern. There are no lesions in the tubules, interstitium, or blood vessels. The deposits stain with anti-IgG and anti-C3 and may exhibit light-chain restriction. The EM picture is pathognomonic: IG deposits consist of thick microtubules (rather than fibrils) 30-50 nm arranged in parallel arrays. Clinical features include hematuria (70%), nephrotic proteinuria (70%), hypertension (65%), and end-stage renal disease (40-50%). IG should be differentiated from FG – both conditions contain non-amyloid (Congo-red negative), organized glomerular immune deposits. Although distinct definitions based on the
fibril morphology have been described, there is a considerable overlap between these 2 entities. For diagnosis of FG and IG, examination with EM is needed. As mentioned above, only a few cases demonstrating monotypic glomerular deposits on IF analysis should be considered to represent MGRS and, thus, warrant further investigation and referral to a hematologist.

MGRS WITH NON-ORGANIZED DEPOSITS

1. MONOCLONAL IMMUNOGLOBULIN DEPOSITION DISEASE (MIDD)

MIDD includes 3 rare conditions associated with the production and deposition of different monoclonal proteins: light-chain deposition disease (LCDD), heavy-chain deposition disease (HCDD) and light-chain and heavy-chain deposition disease (LHCCD). The pattern of deposition, clinical features and prognosis are similar between LCDD, HCDD and LHCCD. LCDD (also called Randall disease) is the most common type of MIDD, usually involving the kappa light chain. Notably, LCDD is associated with MM in 65%. In addition, LCDD is found in 5% of patients with MM. Renal involvement is almost always present in LCDD resulting in proteinuria, renal impairment, and microscopic hematuria. In contrast to AL amyloidosis, MIDD is characterized by early, progressive decline in renal function. Extrarenal manifestations include heart, liver, nerves, spleen, gastrointestinal tract and skin involvement. LCDD has a mean overall survival of 49 months similar to AL amyloidosis. Key diagnostic features in LCDD include thickening of tubular basement membranes, nodular glomerulosclerosis, and expansion of the mesangial matrix due to deposition of amorphous Congo-red negative material. There is light-chain restriction as seen with use of anti-kappa or anti-lambda stains. In HDCC, the glomerular deposits consist of γ, α, or μ heavy-chain, whereas light chain IF is negative and on EM, granular, electron-dense deposits are observed in the glomeruli and tubular basement membranes.

2. C3 GLOMERULOPATHY (C3 GLOMERULONEPHRITIS AND DENSE DEPOSIT DISEASE)

C3 glomerulopathy includes C3 glomerulonephritis and dense deposit disease (DDD). The activation of the alternative pathway of the complement resulting in glomerular aggregation plays a key role in the pathophysiology of C3 glomerulopathy. Some cases of C3 glomerulopathy are associated with the presence of a monoclonal paraprotein in serum and MGUS in the bone marrow. Such cases are thought to represent MGRS, on the basis of laboratory evidence suggesting a causal relationship between a monoclonal immunoglobulin and complement activation. The mechanism by which C3 deposition occurs is not fully understood, however, it has been suggested that the monoclonal immunoglobulin may bind to and inactivate factor H of the complement cascade. The characteristic finding in DDD and C3 glomerulonephritis is a membranoproliferative glomerulonephritis. Mesangial, subendothelial and intracapillary proliferation is common. Staining for C3 is seen in the mesangial and capillary loops but staining for monoclonal immunoglobulins is negative. EM demonstrates a distinctive appearance of “sausage-like” intramembranous deposits in DDD. C3 glomerulonephritis contains less distinctive subendothelial, intramembranous, and subepithelial C3 deposits. Proteinuria, hematuria, and renal insufficiency may be present.

3. PROLIFERATIVE GLOMERULONEPHRITIS WITH MONOCLONAL IGG DEPOSITS (PGNMID)

In PGNMID, a monoclonal immunoglobulin is deposited in the mesangium and along the capillary walls, leading to the activation of the classical pathway of the complement resulting in a capillary-wall remodelling and membranoproliferative glomerulonephritis. PGNMID differs from MIDD because PGNMID is limited in the glomeruli whereas MIDD affects glomeruli as well as tubules. PGNMID has a monoclonal staining pattern whereas other, more common, membranoprolif- erative glomerulonephritis contains polyclonal depositions. The characteristic finding in renal biopsy is a membranopro- liferative glomerulonephritis with monoclonal staining for a single light chain and a single heavy chain. The monoclonal immunoglobulin is usually IgG although IgA PGNMID has also been reported. EM reveals mesangial and subendothelial non-fibrillar electron-dense deposits. PGNMID should be differentiated from cryoglobulinemic glomerulonephritis. Notably, in the majority of patients, the concentration of the monoclonal immunoglobulin is very low in serum so that it is undetectable even on IFX study and a high index of suspicion is required for diagnosis. Bone-marrow examination including flow cytometry immunophenotyping usually reveals the underlying plasma-cell clone.

CONCLUSION

Diagnosis of MGRS requires multidisciplinary input from hematologists, nephrologists, and pathologists. Although rare, a high index of suspicion should be maintained for MGRS. Therefore, all patients with MGUS should have periodic tests of renal function including urinalysis for proteinuria and hematocrit, and hematologists should be alert to early detect any sign of possible renal damage and organize a referral to the renal team. A renal biopsy must always be performed when MGRS is suspected. Recognition of MGRS is important because renal function may improve significantly with appropriate treatment. Although a description of the therapeutic approaches
is not the purpose of this article, it should be mentioned that patients should be treated with chemotherapy targeting the responsible clone, similar to patients with myeloma cast nephropathy. Preservation and restoration of kidney function are possible with successful chemotherapy. In addition to end-stage renal disease, the persistence of the monoclonal gammopathy is associated with high rates of recurrence after kidney transplantation; however, achievement of hematologic response with use of appropriated therapy is able to prevent recurrence after kidney transplantation.

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