Monoclonal gammopathies of renal significance

Authors: Sahana Gnanasampanthan[A] and Andreas Kousios[B]

ABSTRACT

The term monoclonal gammopathies of renal significance (MGRS) encompasses a group of renal histopathological lesions fulfilling two criteria: (a) they are caused by nephrotoxic monoclonal immunoglobulins and (b) the monoclonal immunoglobulins are produced by small B-cell or plasma cell clones which do not meet the criteria for multiple myeloma or malignant lymphoma. Here, we provide a review of the MGRS definition and related terminology and elaborate on the diagnostic approach and treatment principles from the general physician perspective.

Introduction

The kidneys are commonly affected by excessive paraprotein (monoclonal immunoglobulin, MIg) production in symptomatic or high-grade B-cell and plasma cell proliferative disorders, such as multiple myeloma (MM), Waldenström macroglobulinemia and chronic lymphocytic leukaemia (CLL). In some instances, due to the nephrotoxic physicochemical properties of certain paraproteins, the kidneys are affected even when the paraprotein concentration is low, in the context of low-grade B-cell or plasma cell haematological conditions. These conditions include smouldering multiple myeloma (SMM), smouldering Waldenström macroglobulinemia, monoclonal B-cell lymphocytosis (MBL), low-grade CLL and low-grade B-cell non-Hodgkin lymphomas; conditions considered non-malignant or pre-malignant grouped under the term monoclonal gammopathies of undetermined significance (MGUS)[1] (Table 1). Undoubtably, when these conditions cause kidney injury (end organ damage), the term MGUS is a misnomer and prior to 2012 there was no uniform diagnostic classification to guide clinicians.

In 2012 the term monoclonal gammopathies of renal significance (MGRS) was introduced.[2] MGRS discriminates haematological conditions with small B-cell or plasma cell clones causing renal disease from the benign MGUS. The clinical implications are important. MGRS does not fulfil the criteria for MM or symptomatic lymphoma (Table 1) and therefore does not warrant treatment from the haematological standpoint. Nonetheless, if MGRS is left untreated, kidney disease progresses to end-stage kidney disease (ESKD) with significant morbidity and mortality and recurrence after kidney transplantation. Consequently, treatment in MGRS is clone-directed, with regimens commonly used in haematological disease, but the treatment aim is to preserve renal function.

The introduction of the term MGRS expands and improves the classification of paraprotein-related renal disease. It raised awareness, improved collaboration between haematologists, nephrologists and histopathologists and enabled directed treatment for MGRS, which was previously underdiagnosed and undertreated.

MGRS definition

Since 2012, the definition of MGRS evolved and was further refined by the International Kidney and Monoclonal Gammopathy Research Group in 2019.[3]

MGRS is defined as any clonal B-cell or plasma cell lymphoproliferative disorder which fulfils both of the following criteria:

Key points

- Monoclonal gammopathies of renal significance (MGRS) should be suspected if a circulating paraprotein is detected with renal impairment and/or proteinuria.
- Diagnosis of MGRS requires a kidney biopsy (demonstrating monoclonal immunoglobulin related renal pathology) and accurate description of the underlying haematological disease and type of B-cell or plasma cell clone.
- There is a wide spectrum of renal histopathological lesions in MGRS.
- By definition, the underlying haematological disorder does not meet the criteria of multiple myeloma or symptomatic lymphoma. Treatment is clone-directed but the aim of treatment is to preserve renal function.
- Early recognition and treatment in a multidisciplinary setting (histopathologists, nephrologists and haematologists) is recommended to improve patients' outcomes.

KEYWORDS: Paraprotein-related renal disease, monoclonal immunoglobulins, monoclonal gammopathies of renal significance, Bence-jones protein, chronic kidney disease

DOI: 10.7861/clinmed.2023-RM3

Authors: [A]renal fellow, Hammersmith Hospital, Imperial College Healthcare NHS Trust, London, UK; [B]consultant nephrologist, Hammersmith Hospital, Imperial College Healthcare NHS Trust, London, UK and honorary senior clinical lecturer, Imperial College, London, UK

Table 1. Classification and characteristics of haematological disease (B cell and plasma cell proliferative disorders)[3]

Disease	Clone	BMAT	Monoclonal immunglobulin	SPEP/IFEM-spike	Organ involvement
Monoclonal gammopathy of undetermined significance	Any	<10%	Any	<30 g/l	None
Smouldering multiple myeloma	Plasma cell	10–60%	Any	≥30 g/l	None
Multiple myeloma	Plasma cell	≥10%	Any	≥30 g/l	SLiM CRAB: > 60% bone marrow plasma cells > Involved:uninvolved free light-chain ratio >100 > >1 bone lesion on MRI, hypercalcaemia, renal impairment, anaemia and lytic bone lesions
Smouldering Waldenström macroglobulinemia	Lymphoblastic Lymphoma clone	≥10%	IgM	≥30 g/l	None
Symptomatic Waldenström macroglobulinemia	Lymphoblastic Lymphoma clone	≥10%	IgM	≥30 g/l	Anaemia, hyperviscosity, constitutional symptoms, bulky lymphadenopathy, hepatosplenomegaly and neuropathy
Monoclonal B cell lymphocytosis	B cell clone	Peripheral B-cell count $<5 \times 10^9$/l	Any	Any	No lymphadenopathy
Chronic lymphocytic leukaemia	B cell clone	Peripheral B-cell count $>5 \times 10^9$/l	Any	Any	Lymphadenopathy, anaemia and thrombocytopenia
Other B-cell lymphoproliferative disorders	Pan B cell markers (CD19+ CD20+ CD79+ CD22+ PAX5+)	Presence or absence	Any	Any	Lymphadenopathy and splenomegaly

BMAT = bone marrow aspiration and trephine biopsy; SLiM CRAB = symptomatic, light chains, MRI, high calcium, renal dysfunction, anaemia and bony lytic lesions.

1. Kidney lesions on biopsy that are related to the produced monoclonal immunoglobulin (the nephrotoxic MIg) and
2. The underlying haematological condition does not cause tumour complications or meet any of the current haematological indications for specific therapy (Table 1).

The spectrum of renal histopathology in MGRS

Intact monoclonal immunoglobulins are not filtered through the glomerular basement membrane due to their size. The smaller light chains are freely filtered and subsequently reabsorbed and catabolised in the proximal tubular cells. Several modes of nephrotoxicity have been described, including deposition and interaction with resident renal cells, precipitation, and activation of cytokines and complement. Deposited paraproteins in renal tissue may be composed of intact monoclonal immunoglobulin, light chain only, heavy chains, light and heavy chains or truncated parts of these molecules. Renal histopathology may involve any of the four renal compartments (glomeruli, tubules, interstitium and vessels) alone or in combination.[4] The site and pattern of renal injury depends on several factors but most importantly on the individual structural characteristics and physiochemical properties of the paraprotein, which contribute to its nephrotoxic potential at low concentrations.[5]

It is therefore not unexpected that the spectrum of MGRS renal histopathology is wide and includes among others: immunoglobulin-related amyloidosis, monoclonal immunoglobulin deposition disease (MIDD), light chain proximal tubulopathies and cryoglobulinaemic (type I and II) glomerulonephritis (Box 1). Of note, light chain cast nephropathy is a diagnostic feature of MM and therefore it is excluded (by definition) from the MGRS classification.

Correct renal histopathological MGRS classification is the cornerstone of optimal management and requires close collaboration between the experienced renal histopathologist, renal physician and haematologist. This is particularly important for the rare MGRS, where ancillary techniques on renal and bone marrow tissue and imaging are often required for diagnosis.

Box 1. The renal histopathology of MGRS

Immunoglobulin related amyloidosis

- AL amyloidosis (immunoglobulin light chain amyloidosis)
- AH amyloidosis (immunoglobulin heavy chain amyloidosis)
- AHL amyloidosis (immunoglobulin heavy and light chains amyloidosis)

Monoclonal immunoglobulin deposition diseases (MIDD)

- Light chain deposition disease (LCDD)
- Heavy chain deposition disease (HCDD)
- Light and heavy chain deposition disease (LHCDD)

Light chain proximal tubulopathy (LCPT)

Crystal-storing histiocytosis

Type I and Type II (monoclonal) cryoglobulinaemic glomerulonephritis

(Cryo) Crystalglobulin glomerulonephritis

Proliferative glomerulonephritis with monoclonal immunoglobulin deposits (PGNMID)

Immunotactoid glomerulonephritis

Monoclonal fibrillary glomerulonephritis

C3 glomerulopathy with monoclonal gammopathy

Thrombotic microangiopathy – associated with monoclonal gammopathy

Glomerular microangiopathy associated with POEMS syndrome

Miscellaneous

- Anti-GBM disease secondary to monoclonal gammopathy
- Membranous glomerulopathy with light chain restricted deposits

Diagnostic approach in MGRS

MGRS diagnosis cannot be made without a kidney biopsy (demonstrating paraprotein-related pathology) and accurate description of the underlying B-cell or plasma cell clone (see MGRS definition). A nephrologist is often then first point of contact and it is usually the renal biopsy findings which trigger further haematological work-up. In some instances, patients on long-term haematology follow-up for MGUS are referred to the nephrologist to determine renal involvement when they develop proteinuria or renal impairment.

The clinical features of MGRS may provide some clues on the kidney pathology but they are mostly non-specific and should not be used to defer renal biopsy. For example, AL amyloidosis commonly presents with nephrotic syndrome (albuminuria, hypoalbuminaemia and oedema) and relatively preserved renal function without hypertension. MIDD presents with nephrotic syndrome or significant proteinuria and CKD (often due to late diagnosis). Conversely, cryoglobulinaemic (type I or type II) glomerulonephritis may have a more dramatic presentation of rapidly progressive glomerulonephritis (AKI and nephritic syndrome). Light chain proximal tubulopathy manifests with slowly progressive CKD, proteinuria and evidence of tubular dysfunction with Fanconi syndrome (normoglycaemic glycosuria, phosphaturia, uricosuria and proximal tubular acidosis). A high discrepancy between albuminuria and proteinuria indicates the presence of mainly monoclonal light chain (Bence-Jones protein) and low-molecular weight proteins due to a tubular pattern of renal injury and overflow of the paraprotein.

Extra-renal manifestations are not uncommon but are often underdiagnosed. In AL amyloidosis, cardiac involvement confers poor prognosis and nerve involvement may limit the use of effective treatment due to neurotoxicity (ie bortezomib). In MIDD, up to 50% of patients may have at least one extra-renal manifestation (cardiac, liver, central nervous system) but they are often asymptomatic or less symptomatic compared to patients with AL amyloidosis.[6] Cryoglobulinemia is a systemic disease presenting with broad clinical features and severity, including arthralgia, purpura, skin ulcers, neuropathy and life-threatening complications, such as hyperviscosity syndrome in type I cryoglobulin.[7]

The commonest indications for a renal biopsy in MGRS are proteinuria and renal impairment that are otherwise unexplained. It is important to note that MGUS is very common in the general population and its prevalence increases with age; up to 1.7% in ages 50–60, increasing to 6.5% in those older than 80 years.[8] In these age groups, hypertension, diabetes and CKD are also highly prevalent and a circulating paraprotein in the context of MGUS is often co-existent and not the cause of renal disease. Therefore, a patient with small B-cell or plasma cell clone, no proteinuria and normal renal function will not need a kidney biopsy. Similarly, a patient with explained stable CKD/proteinuria and absence of light chain proteinuria may be considered for conservative management and follow-up without a renal biopsy, especially if they are frail or the risks of a biopsy and chemotherapy treatment outweigh benefits.

Two recent studies examined the predictors of finding MGRS lesions in patients who had a positive serum/urine monoclonal test and underwent indication biopsies. Approximately 40% had an MGRS lesion (with AL amyloidosis being the most common). In the remaining 60%, the commonest findings were atherosclerosis and diabetic nephropathy. The predictors of finding an MGRS lesion were elevated serum free light chain (SFLC) ratio, significant proteinuria (>1.5 g/d) and microscopic haematuria.[9,10]

Once MGRS is identified on biopsy, the next step is to establish the haematological diagnosis. Combining serum and urine protein electrophoresis with immunofixation and SFLC ratio increases the sensitivity of detecting the paraprotein close to 100%, with the exception of PGNMID, a rare form of MGRS where a paraprotein is only detected in 30–40% of patients.[11–14] The SFLC ratio should be adjusted in patients with CKD to account for decreased light chain clearance (the 'normal' ratio is 0.26–1.65; the 'renal range' is 0.37–3.17). Urine free light chain is not clinically validated and should not be used.

Bone marrow aspiration and biopsy is performed in almost all patients, though CLL can be diagnosed with flow cytometry from peripheral blood. Ancillary studies on bone marrow (cytogenetics, FISH and next-generation DNA sequencing) provide useful information on prognosis and responsiveness to treatment. If a clone is not identified, imaging with CT/CT-PET or whole-body MR should be considered to look for plasmacytomas or lymphadenopathy in low-grade lymphomas and attempt biopsy of these lesions.

MGRS treatment principles

Cases of MGRS are rare; they comprise a wide spectrum of haematological disease with associated renal pathology and

varying degrees of clinical severity. Consequently, lack of well-contacted prospective studies on the natural history of MGRS with different severity and treatments limits the strength of evidence for treatment recommendations.[15]

Survival is better in MGRS compared to overt haematological malignancies but renal survival is poor. The treatment aim is to preserve renal function, preventing or delaying progression to ESKD. The type of clone determines the treatment regimen. Plasma cell clones are treated with a combination of anti-plasma agents used in MM. The treatment of patients with lymphoplasmacytic and B-cell clones is based on anti-B cell regimens, such as those used in lymphomas, Waldenström macroglobulinemia and CLL.

In our experience, a multidisciplinary group approach involving histopathologists, haematologists and nephrologists improves recognition of MGRS, the clinicians' expertise and the patient's experience and outcomes. For patients with early CKD, significant proteinuria or AKI, aggressive clone-directed treatment should be discussed, with stem cell transplantation where appropriate. For late/advanced CKD, realistic treatment objectives should be set, based on risk versus benefit of drug toxicity and the prospect of renal function recovery and/or preservation. One exception is candidates for renal transplantation, where best haematological response prior to transplantation reduces the risk of recurrence and/or improves allograft survival; therefore, treatment should be considered even in late CKD stages. Older, frailer patients present with particular challenges, where the MDT opinion is valuable.

MGRS continues to evolve. Treatment trials and novel diagnostics are needed. More importantly, prospective collaborative national and international studies like the international K-REG and the UK national registry of rare kidney diseases will improve our understanding and management of MGRS. ■

References

1 Kousios A, Duncan N, Charif R, Roufosse C. Smoldering myeloma presenting with renal histopathology of monoclonal gammopathy of renal significance: adding to the complexity. *J Am Soc Nephrol* 2018;29:2901.

2 Leung N, Bridoux F, Hutchison CA *et al*. Monoclonal gammopathy of renal significance: when MGUS is no longer undetermined or insignificant. *Blood* 2012;120:4292–5.

3 Leung N, Bridoux F, Batuman V *et al*. The evaluation of monoclonal gammopathy of renal significance: a consensus report of the International Kidney and Monoclonal Gammopathy Research Group. *Nat Rev Nephrol* 2019;15:45–59.

4 Kousios A, Roufosse C. An update on paraprotein-related renal pathology. *Diagnostic Histopathol* 2019;25:408–21.

5 Basnayake K, Stringer SJ, Hutchison CA, Cockwell P. The biology of immunoglobulin free light chains and kidney injury. *Kidney Int* 2011;79:1289–1301.

6 Cohen C, Joly F, Sibille A *et al*. Randall-type monoclonal immunoglobulin deposition disease: new insights into the pathogenesis, diagnosis and management. *Diagnostics (Basel, Switzerland)* 2021;11:420.

7 Kousios A, Duncan N, Charif R *et al*. Autologous stem cell transplant for the treatment of type I crystal cryoglobulinemic glomerulonephritis caused by monoclonal gammopathy of renal significance (MGRS). *Kidney Int Reports* 2019;4:1342–8.

8 Kyle RA, Therneau TM, Rajkumar SV *et al*. Prevalence of monoclonal gammopathy of undetermined significance. *N Engl J Med* 2006;354:1362–9.

9 Klomjit N, Leung N, Fervenza F, Sethi S, Zand L. Rate and predictors of finding monoclonal gammopathy of renal significance (MGRS) lesions on kidney biopsy in patients with monoclonal gammopathy. *J Am Soc Nephrol* 2020;31:2400–11.

10 Yong ZH, Yu XJ, Liu JX *et al*. kidney histopathologic spectrum and clinical indicators associated with MGRS. *Clin J Am Soc Nephrol* 2022;17:527–34.

11 Nasr SH, Satoskar A, Markowitz GS *et al*. Proliferative glomerulonephritis with monoclonal IgG deposits. *J Am Soc Nephrol* 2009;20:2055–64.

12 Bhutani G, Nasr SH, Said SM *et al*. Hematologic characteristics of proliferative glomerulonephritides with nonorganized monoclonal immunoglobulin deposits. *Mayo Clin Proc* 2015;90:587–96.

13 Gumber R, Cohen JB, Palmer MB *et al*. A clone-directed approach may improve diagnosis and treatment of proliferative glomerulonephritis with monoclonal immunoglobulin deposits. *Kidney Int* 2018;94:199–205.

14 Kousios A, Duncan N, Tam FWK *et al*. Proliferative glomerulonephritis with monoclonal Ig deposits (PGNMID): diagnostic and treatment challenges for the nephrologist! *Kidney Int* 2019; 95:467–8.

15 Fermand JP, Bridoux F, Kyle RA *et al*. How I treat monoclonal gammopathy of renal significance (MGRS). *Blood* 2013;122:3583–90.

Address for correspondence: Dr A Kousios, West London Renal and Transplant Centre, Du Cane Rd, Hammersmith Hospital, Imperial College Healthcare NHS Trust, W10 0HS.
Email: a.kousios@imperial.ac.uk; andreaskousios@gmail.com
Twitter: @AndreasKousios1