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NEPHROLOGY – REVIEW

Monoclonal gammopathy of renal significance (MGRS): the characteristics and significance of a new meta-entity

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Abstract Monoclonal gammopathy of renal significance (MGRS) is a new nosological group of entities (meta-entity) defined in 2012, whose pathogenesis depends on monoclonal immunoglobulins (Ig) secreted by low-grade lymphoproliferative disorders, which belong to M-protein-related diseases. Renal damage is the result of monoclonal Ig deposit or its activity as autoantibodies, which can compromise any nephronal area. MGRS does not include kidney diseases produced by high-grade lymphoproliferative disorders as well as those whose pathogenesis are independent of monoclonal Ig (such as drug toxicity or metabolic disorders). The importance of this hemato-nephrological meta-entity is based on two aspects: First, it is associated with increased morbidity and mortality, including recurrence in post-renal transplant or its appearance as "de novo" after it; and second, it usually improves after treating the plasmocyte or lymphocyte clone responsible, leading to the elimination of M-protein. Between low-grade lymphoproliferative disorders, monoclonal gammopathy of undetermined significance (MGUS) requires special consideration for two reasons: First, it is the disorder most related to MGRS; second, when MGUS progresses to MGRS, effective treatment against toxic underline clone should be performed taking into account the nephrological perspective.

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Introduction

Monoclonal gammopathy of renal significance (MGRS) has been recently delineated in 2012 and consists of a new group of hemato-nephrological entities (meta-entity) characterized by renal damage mediated by monoclonal immunoglobulin (Ig) secreted by low-grade lymphoproliferative disorders, mainly monoclonal gammopathy of undetermined significance (MGUS). This hemato-nephrological meta-entity belongs to M-protein-related diseases whose pathogenesis depends on monoclonal Ig. MGRS kidney damage is induced by either monoclonal Ig deposition in renal tissues or by its activity as autoantibody. MGRS includes a high spectrum of nephropathies that could compromise any nephronal structure: glomeruli, tubulointerstitial and/or renal vessels. Finally, those nephropathies linked to high-grade lymphoproliferative disorders have been excluded from MGRS, as well as, those whose lesion is independent of monoclonal Ig such as drug toxicity or metabolic disorders [1–3].

The importance of considering MGRS as a particular nosological group is based on the following reasons: Firstly, this meta-entity is associated with an increased morbidity and mortality, included its recurrence in post-renal transplant period and even as "de novo" presentation; and secondly, MGRS usually improves after performing any lymphoproliferative treatment, such as chemotherapy, radiotherapy or stem cells transplantation. It is worth mentioning that some MGRS, especially those related to MGUS, is not usually treated even though effective treatment against toxic underline clone should be performed taking into account the nephrological perspective [2, 4–9].

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MGRS: pathophysiology, histopathology and clinical presentation

Two major pathophysiologic mechanisms, which mainly depend on monoclonal Ig physicochemical characteristics, have been involved in MGRS. The most frequent of them is renal injury induced by monoclonal Ig deposition. It is preceded by receptor-mediated endocytosis into glomerular or tubular cells after monoclonal Ig has been filtrated into urinary space. The other mechanism depends on monoclonal Ig acting as autoantibody, as are the case of C3 glomerulopathy (C3G) and atypic hemolytic uremic syndrome (aHUS), where antibodies produce dysregulation of liquid or solid phase of the alternative pathway of complement, for instance anti-factor H is the main antibody involved in C3. The latter mechanims have also been reported in C4 dense deposit disease (C4 DDD) with dysregulation of the mannose-binding lectin pathway of complement, and membranous nephropathy (MN). Pathogenic monoclonal Ig abnormalities have come from hematologic cells mutations [2, 5, 6, 8, 10–17].

Renal biopsy is crucial for diagnosing MGRS because of the broad spectrum of renal diseases which can induce this meta-entity. It has been demonstrated that despite the fact that glomerular and tubulointerstitial areas are the most affected in MGRS, renal vessels can also be involved. Monoclonal Ig deposits could be organized or not, and could compromise glomeruli and/or tubulointerstitial areas, as well as vessels. Monoclonal Ig could be present as a complete or truncated molecule (heavy or light chains). Lambda light chains (LCs) are mostly present in organized deposits, whereas kappa LCs are mostly present in not-organized deposits; kappa LCs are also the most frequently found ones when the implicated pathophysiology is based on autoantibodies. In those cases where conventional renal biopsy is not enough to specify the sort of renal involvement, the immunoelectron microscopy or laser microdissection with mass spectroscopy-based proteomic analysis is useful in order to achieve a more accurate diagnosis [2, 6–9, 11–16, 18, 19, 21].

The diagnostic clue is to determine whether the nephropathy under evaluation is a MGRS, a different renal disease or even a combination of both entities.

Many glomerulopathies have been reported as MGRS, such as renal amyloidosis (included light chain, heavy chain and heavy and light chains amyloidosis), fibrillar glomerulopathy, immunotactoid glomerulopathy (ITG), type I and type II cryoglobulinemic glomerulonephritis (CG), Randall-type monoclonal Ig deposition disease (MIDD) (included light chain, heavy chain and heavy and light chains deposition disease), proliferative glomerulonephritis with monoclonal Ig deposits (PGNMD), membranoproliferative glomerulonephritis (MPGN) associated with monoclonal Ig, MN secondary to monoclonal Ig, C3G associated with monoclonal Ig and C4 DDD associated with monoclonal Ig. Not-organized deposits have been documented in IMDD and PGNMID and could be found in C3G and MN but without pathogenic meaning in the two latter. Truncated monoclonal Ig chains have been found in amyloidosis and IMDD. Additionally, a recently described entity, podocytic infolding glomerulopathy has been associated with multiple myeloma (MM) and could be related to others forms of plasma cell dyscrasias [2, 8, 10, 22].

Tubulointerstitial diseases that have been described as MGRS include light chain Fanconi syndrome (LCFS), light chain proximal tubulopathy without crystals and crystal-storing histiocytosis [2, 3, 23].

MGRS with intra-renal vascular lesions has been found in thrombotic microangiopathies like aHUS. Tubulointerstitial and vascular deposits can also be found in entities with glomerular compromise, such as amyloidosis. Cast nephropathy has not been reported as MGRS, since this entity is associated with high tumor burden which produces high serum levels of free light chains (FLC) leading to saturation of tubular megalin–cubilin complex, high concentration of FLC in the urine and consequently appearance of intratubular cast (Table 1) [2, 4, 5, 15, 17, 24].

MGRS can clinically present as any of the classical nephrologic syndromes, and it is important to characterize the underlined pathologic clone in order to evaluate the benefit of performing its treatment [1, 2, 4–6, 25].

Monoclonal Ig detection

Monoclonal Ig detection can be performed by different sort of assays, such as serum and urine protein electrophoresis, immunofixation and FLC immunoassay. Protein electrophoresis allows to quantify M-component while serum FLC ratio is the most reliable (sensitive and specific) of these assays. However, immunofixation is more sensitive when there are small clones because they usually produce intact immunoglobulins rather than FLC. Finally, urine FLC is an unreliable method due to the variable LCs handling by glomeruli and tubules [1, 2, 20, 24].

Normally, FLC exist because there is overproduction of LCs with respect to heavy chains. Even though kappa chain production exceeded lambda chain production, their serum ratio is defined by their clearance. Under normal conditions, LCs clearance is mainly performed by the kidney, and since kappa chains are monomeric they are cleared more quickly than lambda chains which are dimeric; consequently, normal serum FLC ratio has an average value of 0.6 (0.26–1.65). When glomerular filtration rate (GFR) declines, LCs clearance performed by reticuloendotelial system increases and half-life and serum concentration of LCs increase, too.

Table 1 Classification of monoclonal gammopathy of renal significance (MGRS)

Glomerulopathies	Tubulointerstitial diseases	Intra-renal vascular lesions
Renal amyloidosis	*Light chain Fanconi syndrome (LCFS)*	*Atypic hemolytic uremic syndrome (aHUS)*
Light chains amyloidosis (AL amyloidosis)	*Light chain proximal tubulopathy without crystals*	
Heavy chains amyloidosis (AH amyloidosis)	*Crystal-storing histiocytosis*	
Heavy and light chains amyloidosis (AHL amyloidosis)		
Fibrillar glomerulopathy (FGN)		
Immunotactoid glomerulopathy (ITG)		
Cryoglobulinemic glomerulonephritis (CG)		
Type I and type II CG		
Randall-type monoclonal Ig deposition disease (MIDD)		
Light chain deposition disease (LCDD)		
Heavy chain deposition disease (HCDD)		
Heavy and light chain deposition disease (HLDD)		
Proliferative glomerulonephritis with monoclonal Ig deposits (PGNMD)		
Membranoproliferative glomerulonephritis (MPGN) associated with monoclonal Ig		
Membranous nephropathy (MN) secondary to monoclonal Ig		
C3 glomerulopathy (C3G) associated with monoclonal Ig		
C4 dense deposit disease (C4 DDD) associated with monoclonal Ig		

Moreover, patients who suffer even a mild GFR reduction, present an increased serum FLC ratio of polyclonal LCs, without any polyclonal or monoclonal underlying disorder. In consequence, as well as the GFR decreases, the normal serum value of FLC ratio changes, becoming higher than in other populations; in this group, the normal average value is 1.1 and the range is between 0.37 and 3.17. It is worth pointing out that GFR reduction secondary to aging also increases normal serum FLC ratio values. Regarding that an elevation in FLC ratio indicates a monoclonal kappa chain disorder, while a decreased ratio indicates a monoclonal lambda chain one. It is crucial to take into account the GFR value when considering serum FLC in order to avoid a monoclonal kappa chain overdiagnose or a monoclonal lambda chain underdiagnose [3, 24, 26–28].

MGRS and MGUS

Among low-grade lymphoproliferative disorders, MGUS requires a particular consideration: First of all, it is the low-grade lymphoproliferative disorder most frequently related to MGRS; and secondly, when MGUS progresses to MGRS it is currently not treated.

MGUS is one of the most common pre-malignant disorders, and it is defined by a M-protein less than 30 g/L (or an abnormal ratio of serum FLC kappa/lambda), bone marrow (BM) with plasma cell percentage <10%, and absence of signs or symptoms related to MM (CRAB: high serum calcium, renal insufficiency, anemia or bone lesions) or other lymphoproliferative malignancies such as Waldenström's macroglobulinemia (WM). Regarding IgM MGUS, there is some controversy concerning its diagnostic criteria. In the Second International Workshop on WM, a consensus panel defined IgM MGUS by the presence of an IgM M-protein (irrespective of IgM concentration) without bone marrow infiltration by lymphoplasmacytic lymphoma, whereas the Mayo Clinic criteria requires less than 10% BM involvement and IgM M-protein less than 30 g/L. Diagnosis of LCs MGUS (20% of MGUS) is based on an abnormal ratio of serum FLC kappa/lambda in the context of no peak of monoclonal heavy chains [5, 24, 29–32].

The importance of diagnosing MGUS is based on its increased risk of developing a hematologic malignancy and also on the fact that a small clone can also be responsible for producing toxic M-proteins which can induce MGRS or another M-protein related disease. Since by definition, a patient suffering from MGUS has no renal lesion, if any kidney damage is detected and depends on monoclonal Ig, then MGUS diagnosis should be changed to MGRS due to the renal pathophysiological significance of this hemato-nephrological entity [1, 2, 24, 33, 34].

MGUS has an annual risk of progression to light chain amyloidosis of around 1% (most of them with renal disease). More than 50% of patients with MPGN associated with monoclonal Ig have MGUS. Twenty-seven percent

of patients with LCFS secondary to monoclonal Ig have MGUS. Thirty-one percent of adult patients with C3G have monoclonal Ig, and half of them have MGUS. Most of ITG are associated with monoclonal Ig, and in one third of the type I CG, glomeruli are compromised but most of the renal involvement has been observed in type II CG. It is worth mentioning that most of the literature refers to MGUS and renal disease, not to MGRS which is currently its correct denomination [1–4, 11, 23, 33, 35–37].

MGUS can regress, which has been documented in 2–5% of cases, most of them had low initial concentrations of M-proteins and suffered from autoimmune or infectious diseases. Moreover, MGUS may develop after renal transplantation and could also be of primary or secondary origin, the latter related to MM treatment [3, 5].

The follow-up of MGUS patients is based on Mayo Clinic risk stratification model which has been made considering its probability of progression to malignant disease. This model stratified this entity in three risk groups: low, intermediate and high, and is based on three risk factors: M-protein $\geq$1.5 g/dl, type of monoclonal Ig (non-IgG) and abnormal FLC ratio. Sixty percent of these patients present intermediate or high risk. Patients with a life expectancy $\geq$5 years should have their first control in 6 months and then continue annually, except for low-risk patients who could be evaluated every 2 years. Those patients with a life expectancy <5 years are considered not to benefit with medical follow-up. The current follow-up includes interview, physical examination and laboratory tests: quantification of M-protein, complete blood count, serum creatinine and calcium; albuminuria is measured in patients with high FLC levels, since there is high prevalence of MGRS in this group [5].

A more complete renal evaluation is needed in order to achieve an early diagnosis of MGRS. For instance, tubular damage markers are very important since LCFS is one of the earlier manifestations of MM and one third of monoclonal LCFS has hematologic diagnostic of MGUS so it is possible that even one of the earlier manifestation of MGRS could be monoclonal LCFS or other tubular dysfunction [23, 38].

The prevalence of MGUS is 3.2% in people older than 50 years but increase to 5.3% after seventies. It has been estimated that M-protein-related diseases (mainly MGRS and cardiac amyloidosis) are present in 10% of patients with hematologic diagnosis of MGUS. MGRS prevalence would be around 0.32 and 0.53% depending on the population age. However, these numbers could be even higher since MGRS is an understudied group of nephropathies. Thus, it is crucial to keep in mind a nephrological perspective during the MGUS evaluation [29, 33, 34].

Conclusion

Patients who suffer from MGUS and also renal disease of undetermined origin should be submitted to renal biopsy in order to clarify their renal diagnosis, of course if this procedure is not contraindicated. The diagnostic clue is to determine whether the nephropathy under evaluation is MGRS, a different renal disease or even a combination of both entities. Conversely, renal disease can be the initial manifestation of an undiagnosed low-grade lymphoproliferative disorder. Thus, MGRS represents a new challenge which demands interdisciplinary evaluation.

Compliance with ethical standards

Conflict of interest All the authors declare that they have no conflict of interest.

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