COMMENT

Port J Nephrol Hypert 2018; 32(4): 399-401 • Advance Access publication 4 January 2019

Kidney biopsy in monoclonal gammopathies

Isabel Mesquita[1], Mário Góis[2,3]

[1] Nephrology Department, Hospital Professor Doutor Fernando Fonseca
[2] Nephrology Department, Hospital de Curry Cabral, Centro Hospitalar de Lisboa Central
[3] Laboratory of Renal Morphology, Nephrology Department, Hospital Curry Cabral – Centro Hospitalar de Lisboa Central

Received for publication: Dec 16, 2018
Accepted in revised form: Dec 20, 2018

Several clinical cases have been published in recent issues of PJNH, addressing the monoclonal gammopathies: *Immunoglobulin G4-related disease mimicking multiple myeloma*[1], *Light chain deposition disease: atypical associations in a rare disease*[2] and *What seems most likely may not be the case*[3]. Although these cases have a common denominator – the diagnosis of monoclonal gammopathy – they all had different clinical presentations.

Monoclonal gammopathy of unknown significance (MGUS) is a premalignant condition characterized by the presence of monoclonal gammopathy (requires the serum monoclonal (M) protein <30g/L and bone marrow plasma cells <10%), in a patient without end-organ damage[4].

A wide spectrum of renal disorders may occur in patients with monoclonal gammopathies and all the compartments of the kidney may be affected: glomeruli, blood vessels, tubules and interstitium[5]. Except for myeloma cast nephropathy, which is invariably diagnosed in the setting of symptomatic multiple myeloma (MM), there are other renal conditions related to deposition or precipitation of a monoclonal immunoglobulin (MIg) in patients with indolent B-cell clone – the so-called dangerous small B-cells clones[6]. Thus, in these cases of renal disease due to monoclonal gammopathy, there is end-organ damage and the term "of unknown significance" is inaccurate. Hence, the concept of monoclonal gammopathy of renal significance (MGRS) has emerged. This was introduced by the International Kidney and Monoclonal Gammopathy Research Group (IKMG) in 2012[7], and comprises a group of heterogeneous renal diseases induced by MIg or its components (light and/or heavy chains), produced by B-cell clones, that do not meet the classic hematologic criteria for symptomatic MM or lymphoproliferative disorder. The goal is to differentiate patients with MGUS, who have no evidence of end-organ damage, from patients with monoclonal gammopathy and kidney damage induced by MIg deposition in renal tissue or by its activity as autoantibody in rare cases of C3 glomerulopathy[8].

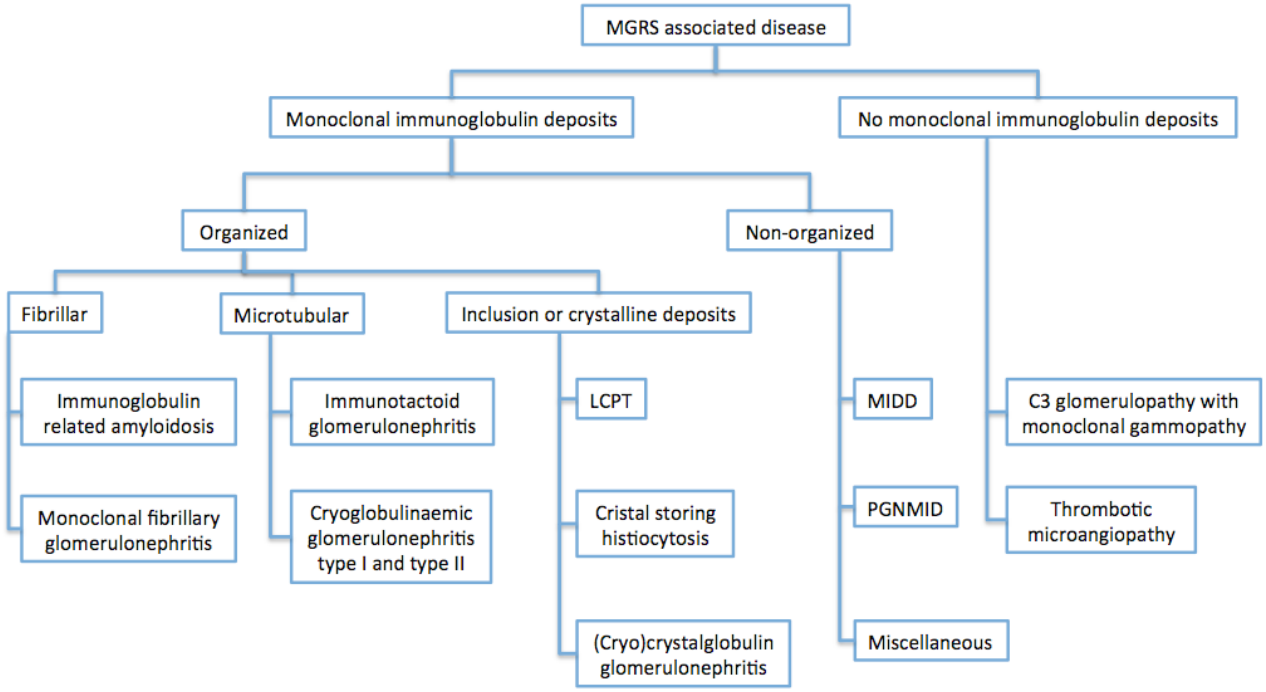
The group of disorders associated with MGRS is heterogeneous, but there is a common link between them: the presence of monoclonal deposits in the kidney, indicating the presence of any underlying clone of lymphocytes or plasma cells, irrespective of the "tumor burden"[8].

The classification scheme proposed by the IKMG for MGRS-associated lesions (Figure 1) is based on the findings of immunofluorescence studies and the ultrastructural appearance of the deposits on electron microscopy. Light microscopy and immunofluorescence studies with a full panel of antibodies are invariably required for assessment of MGRS-associated disorders. However, according to IKMG recommendations, electron microscopy, not being universally available, is not mandatory for valuation of MGRS[9].

The spectrum of MGRS encompasses a variety of renal lesions which was initially classified according to deposits type: organized, non-organized and non-immunoglobulin[5]. At the 2017 in IKMG meeting subcategories were added to the non-organized and non-immunoglobulin classifications: thrombotic microangiopathy associated with monoclonal gammopathy was added as a subcategory of non-immunoglobulin deposits, and a miscellaneous subcategory was added to the non-organized deposit category, which applies to pathological entities that are ultrastructurally similar to a non-monoclonal-immunoglobulin-related disease but

Figure 1

Classification of MGRS-associated renal lesions. Adapted from Leung N et al. The evaluation of monoclonal gammopathy of renal significance: a consensus report of the International Kidney and Monoclonal Gammopathy Research Group[9]



MGRS – Monoclonal gammopathy of renal significance; LCPT – light-chain proximal tubulopathy; MIDD – monoclonal immunoglobulin deposition disease; PGNMID – proliferative glomerulonephritis and monoclonal immunoglobulin deposits.

are only, occasionally, associated with a monoclonal gammopathy[9].

Screening for monoclonal immunoglobulin and an appropriate hematologic workup are fundamental; however kidney biopsy is a key diagnostic tool in the presence of monoclonal gammopathy and unexplained kidney disease, especially in patients aged <50 years with MGUS and renal manifestations (given the low frequency of MGUS in this population). Furthermore, kidney biopsy must also be performed in older individuals with MGUS and signs of renal involvement, as most MGRS-related diseases occur mainly in the elderly[10]. Kidney biopsy is essential to establish the correlation between lesions and monoclonal gammopathy, as the presence of a monoclonal protein, frequent in the elderly, is not by itself equal to the causative agent. This approach is fundamental to minimize misdiagnosis, mainly in amyloidosis[5].

In addition to assessing the MGRS type, kidney biopsy also provides valuable information about the severity of renal disease. It also plays a key role even in advanced chronic kidney disease in which renal transplantation is a future possibility, because of the high possibility of recurrence that the patient faces after the transplant, mainly in the absence of control of the underlying clone[5].

Costa et al[2] reported a case of a patient with the diagnosis of MM and IgG4-related disease. To best of our knowledge, there is no pathologic association between these two conditions. In this case, nephrology consultation and kidney biopsy were made 3 years after the successful treatment of MM. In our opinion, it would have been interesting to elucidate, at the time of diagnosis of MM, if there was evidence of renal involvement and if the renal lesions were caused by IgG4-related disease and/or MM.

Correia et al described a patient with monoclonal gammopathy IgG kappa, type II cryoglobulinemia and hypocomplementemia, diagnosed with light chain deposition disease. The association of type I cryoglobulinemia and monoclonal gammopathy is well described in literature, but there are few reports of

type II cryoglobulinemia associated to monoclonal gammopathy. We would like to emphasize that this patient has a small dangerous B-cell clone, with low tumor burden (<1% bone marrow plasma cells), but the renal lesions were remarkable. On the other hand, in a manuscript published by Cardoso et al[3], although the clinical presentation was quite similar, the pathological findings were distinct. This reinforces the importance of kidney biopsy to make a correct diagnosis, which provides a definitive evidence of end-organ damage, crucial to initiating treatment.

The nephrology community's growing interest in MGRS has led to the recent publication of a consensus document by IKMG[9] which highlights the complexity of this entity and suggests new diagnostic tools such as flow cytometry to identify small clones, genetic tests and fluorescent in situ hybridization studies. An in-depth knowledge of this entity, from clinical presentation to histological findings, will allow an improvement in treatment and prognosis of these patients.

It is worth mentioning that we should reinforce our relationship with hematology to provide this challenging patient group with an adequate management and therapeutic approach.

Disclosure of potential conflicts of interest: None declared

References

1. Costa MS, Silva A, Costa L et al. Immunoglobulin G4-related disease mimicking multiple myeloma. Port J Nephrol Hypert 2018;32(3):283-288.
2. Cunha I, Silva S, Henrique R, Costa M. Light chain deposition disease: atypical associations in a rare PJNH disease. Port J Nephrol Hypert 2018;32(3):289-292.
3. Cardoso F, Marques J, Mendes M, Góis M, Sousa H, Nolasco F. What seems most likely may not be the case. Port J Nephrol Hypert 2018;32(3):305-308.
4. Correia S, Santos S, Martins LS, Santos J. Diagnosis of monoclonal gammopathy of renal significance. Port J Nephrol Hypert 2018; 32(1):52-56.
5. Bridoux F, Leung N, Hutchison CA, et al. International Kidney and Monoclonal Gammopathy Research Group. Diagnosis of monoclonal gammopathy of renal significance. Kidney Int 2015;87(4):698-711.
6. Merlini G, Stone MJ. Dangerous small B cell clones. Blood 2006; 108(8):2520-30.
7. Leung N, Bridoux F, Hutchison CA et al. Monoclonal gammopathy of renal significance: when MGUS is no longer undetermined or insignificant. Blood 2012;120(22):4292-4295.
8. Sethi S, Rajkumar SV, D'Agati VD. The complexity and heterogeneity of monoclonal immunoglobulin–associated renal diseases. J Am Soc Nephrol 2018;29(7):1810-1823.
9. 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 2018; *advanced access publication*.
10. Paueksakon P, Revelo MP, Horn RG, Shappell S, Fogo AB. Monoclonal gammopathy: significance and possible causality in renal disease. Am J Kidney Dis 2003;42:87-95.

Correspondence to:
Isabel Mesquita, MD
Nephrology Department, Hospital Porfessor Doutor Fernando da Fonseca, Amadora, Portugal
E-mail: imesquita@sapo.pt