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Editorial

Monoclonal Gammopathy of Renal Significance: Why is it Signicant?

Ana Cabrita*
NephrologyDepartment, Centro Hospitalar do Algarve, Portugal

***Corresponding author:** Ana Cabrita, Nephrology Department, Centro Hospitalar do Algarve, Faro Unit, Portugal, Rua Leão Penedo, 8000-386, Faro, Portugal, Email: anacabrita2@gmail.com

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Editorial

Monoclonal Gammopathy of Renal Significance (MGRS) is an entity recently emerging. It can be defined as a causal relationship between a small B-cell clone and renal damage[1], usually through the deposition of the secreted Monoclonal Immunoglobulin (MIg) or its fragment [1,2], and not directly related to cellular proliferation [2].

The majority of MGRS are the result of the deposition of the MIg fragment with distinct location and pattern of ultra structural organization [2]. The resultant glomerulopathies can have organized deposits or non-organized deposits. Those with organized deposits can be either fibrillar like immunoglobulin light chain (AL), immunoglobulin Heavy chain (AH) and immunoglobulin Light and Heavy chain (ALH) amyloidosis or micro tubular, such as in type I and type II cryoglobulinemias and immunotactoid glomerulopathy [2]. Randall type monoclonal immunoglobulin deposition disease and non-Randall type proliferative glomerulonephritis with monoclonal immunoglobulin deposits are examples of glomerulopathies with non-organized deposits [2]. Also, in MGRS, deposits of different ultra-structural patterns derived from the same MIg can occur.

Light-chain proximal tubulopathy (with or without Fanconi syndrome) can also be included in MGRS [3,4,5].

Myeloma cast nephropathy, which almost always complicates high tumor mass myeloma, should not be included in MGRS [2], as should not be considered as MGRS nonamyloidfibrillary glomerulonephritis because it is characterized by polyclonal IgG deposits without a detectable clonal B-cell disorder [6,7].

The term MGRS was, in fact, introduced to make a distinction from Monoclonal Gammopathy of Undetermined Significance (MGUS).

MGUS is a plasma cell disorder present approximately 3, 5% of the general population aged 50 years or older [8,9] and is a condition characterized by the presence of a monoclonal Gammopathy without end organ damage [8]. MGUS requires the serum Monoclonal (M) protein to be < 3g/dL and bone marrow plasma cells to be <10% and most importantly there can be no end organ damage attributable to the plasma cell dyscrasia [1]. Currently 3 distinct clinical types of MGUS are identified: non-IgM (IgGor IgA) MGUS, IgM MGUS and light-chain MGUS. Each of this clinical subtype is characterized by unique intermediate stages and progression events [10].

MGUS is one of the most common pre-malignant disorders with an average risk of progression to Multiple Myeloma (MM) or, to a lesser extent, other lymphoproliferative disorders or AL amyloidosis, of 1% per year [11,12]. Typically, patients with IgG or IgA MGUS progress to MM and patients with IgM MGUS progress to Waldenstrom´s Macroglobulinemia (WM) or other lymphoproliferative disorders [13]. Light-chain MGUS is the precursor of light-chain MM and is defined by an abnormal κ/λ free light chain ratio, increase in concentration of the involved light-chain and absence of expression of a monoclonal peak of immunoglobulin heavy-chain in the serum on immunofixation [9].

What is the purpose of making this distinction? Mainly because treatment is not recommended for MGUS but treatment is fundamental in MGRS.

In the majority of cases, the overall survival of patients with MGRS is significantly better than that of MM, except for patients with AL amyloidos is with cardiac involvement in which death can occur rapidly [14]. However, renal outcomes are not [1]. In addition to End-Stage Renal Disease (ESRD), the persistence of the monoclonal Gammopathy is associated with high rates of recurrence after kidney transplantation in MGRS kidney diseases [1,2]. This is one of the most relevant clinical features and is associated with significant morbidity [1].

In MGRS-related kidney diseases treatment is mandatory and sometimes urgent to prevent renal deterioration. Treatment of MGRS should also be considered in patients with ESRD without other organ involvement if the patient is being considered for kidney transplantation [1], because the risk of patients dying from their clone is rare [2]. However, there are no data to suggest that small B-cell clones are truly curable and so the risk of disease recurrence imposes a risk of graft failure [2].

Indeed, treatment of MGRS is often indicated more to preserve Kidney function and prevent recurrence after Kidney transplantation rather than the prolongation of life [2].

In a patient if MGRS is suspected it is mandatory to assess the characteristics of the monoclonal Gammopathy, namely its isotype and whether it corresponds to an overt lymphoid and/or plasmacytc disorder [2]. Restriction to a single class of light chain and/or heavy chain is mandatory[1]. Monoclonal protein studies should be performed to match the monoclonal protein in circulation with the monoclonal deposits present in the Kidney [1]. As MGRS may exhibit low levels of circulating monoclonal protein, immunofixation should be performed along with protein electrophoresis and serum free light chain assay to increase sensitivity [15]. Monoclonal protein studies should be performed on all patients with MGRS-associated

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lesions, even those that are rarely associated with MGRS. The origin of the monoclonal protein should be identified. In the bone marrow, establishing clonality of plasma cells or lymphocytes is essential. The clone must exhibit the same light chain restriction as the circulating monoclonal protein and deposits in the kidney [1]. It is essential to assess the type of nephropathy and its impact on renal function. To accurately characterize the renal disease, a Kidney biopsy with detailed immunofluorescence and electron microscopic studies to identify deposit composition and pattern of organization is needed in most cases. Finally, it is mandatory to carefully search for extra renal manifestations [2].

There are few clinical trials for MGRS-related diseases, except in AL amyloidosis. Therefore, treatment recommendations are based in clinical data obtained from treatment of the clonal disorder in its malignant state [2].

The treatment of MGRS should be tailored to the clone responsible. Although innovative treatment strategies are currently in early clinical testing, to date, no strategy is available to inhibit MIg tissue deposition or to directly clear the already deposited material. So, targeting the underlying B-cell clone with chemotherapy, although it is not a malignant clone per se, is the only available therapeutic option for MGRS [2].

The choice of chemotherapeutic agents should take into account their renal metabolism and potential renal and extrar renal toxicity [2]. For example, cyclophospamide has lower toxicity in patients with reduced kidney function when compared to melphalan [16]. Similarly, thalidomide may be more appropriate than lenalidomide, because the latter as renal clearance and can worsen renal function in some disease states, particularly in AL amyloidosis [17]. Drug agents like bortezomib, rituximab and other CD20 monoclonal antibodies poses no concerns in patients with renal impairment, including ESRD [2]. High dose melphalan supported by autologous peripheral blood stem cell transplantation may be a therapeutic option in some patients. These are some therapeutic options aiming for hematologic stringent complete remission, the goal of therapy.

When treating the renal disease, MGRS should be monitored according to usual best practices, including, for example, control of hypertension and proteinuria preferably with blockers of the renin-angiotensin system, and thrombotic and infectious risk prevention in case of nephrotic syndrome.

MGRS is really an important entity, and significant in our opinion, because it imposes treatment purposes and goals that should be viewed differently, not limited to preservation of life but including organ preservation, in this case the kidney. In this area there is a lot more to learn and discover, and we invite you to share your clinical cases and experiences.

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