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MONOCLONAL GAMMOPATHY OF RENAL SIGNIFICANCE: A LOOK AT THE CURRENT

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ABSTRACT

Introduction: Monoclonal gammopathy of renal significance comprises a spectrum of renal diseases caused by nephrotoxic monoclonal immunoglobulins, secreted by B clones or plasma cells with low tumor burden, which do not meet the diagnostic criteria for hematological neoplasms. Although these clones do not constitute classic malignancies, they have a high capacity to promote clinically significant renal lesions. **Objective:** To conduct a narrative review of the literature on monoclonal gammopathy of renal significance with emphasis on its pathophysiological mechanisms, histopathological classification, diagnostic approach, and emerging therapeutic strategies. **Methods:** A literature review was conducted in the PubMed and SciELO databases, covering publications from the last ten years. Systematic review articles, international clinical guidelines, and original studies with relevance to nephrological practice were prioritized. **Results:** Monoclonal gammopathy of renal significance includes a variety of renal lesions, such as glomerulopathies associated with monoclonal immunoglobulins, tubulointerstitial lesions, and vascular impairments. Renal biopsy remains the gold standard for diagnosis, being essential for defining the histopathological pattern and for therapeutic stratification. The treatment aims at the eradication of the producer clone, using therapies inspired by the protocols of multiple myeloma and B-cell lymphomas, with emphasis on proteasome inhibitors and monoclonal antibodies. Growing evidence indicates that early intervention with clone-directed therapies is associated with stabilization or improvement of renal function. **Discussion:** Monoclonal gammopathy of renal significance represents an entity of increasing clinical relevance, whose evolution can culminate in end-stage chronic kidney disease. Early recognition of the condition, coupled with a multidisciplinary approach involving nephrologists and hematologists, is key to mitigating progressive kidney damage. The absence of established hematologic malignancy does not exclude the need for aggressive treatment, in view of the nephrotoxic impact of monoclonal immunoglobulins.

Keywords: Monoclonal gammopathy of renal significance. Nephrotoxicity. Paraproteinemia. Clone-directed therapy. Renal biopsy.

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1 INTRODUCTION

Monoclonal gammopathies constitute a heterogeneous group of conditions characterized by clonal proliferation of B cells or plasma cells, with consequent production of monoclonal immunoglobulins or fragments thereof, generically called M components. Traditionally, these disorders were associated with hematological neoplasms such as multiple myeloma (MM), Waldenström's macroglobulinemia (WM), and chronic lymphocytic leukemia (CLL), in which neoplastic clones produce monoclonal immunoglobulins with the potential to compromise several organs and systems, including the kidneys [1,2].

However, recognition has emerged that hematological clones with low tumor burden, which do not meet the diagnostic criteria for malignancy, can secrete immunoglobulins with nephrotoxic capacity. This phenomenon culminated in the conceptualization of monoclonal gammopathy of renal significance (MGRS), a clinical entity that lies between monoclonal gammopathy of undetermined significance (MGUS) and classical plasmacytic dyscrasias [1,3].

MGRS is characterized by kidney lesions directly induced by monoclonal immunoglobulins derived from non-malignant but pathogenic B clones or plasma cell cells. Unlike MGUS, whose course is usually indolent, MGRS presents clinically aggressive behavior from the nephrological point of view, with potential evolution to chronic kidney disease and the need for renal replacement therapy [4].

Histological patterns are widely variable and range from glomerulopathies, such as proliferative glomerulonephritis with monoclonal immunoglobulin deposits (PGNMID), to tubulointerstitial lesions, such as proximal light chain tubulopathy (TPLC), as well as smaller-scale vascular involvement [2,5].

The clinical relevance of MGRS lies not only in its association with progressive renal dysfunction, but also in the high risk of recurrence after kidney transplantation. In this context, early diagnosis and characterization of the producing clone are imperative, as they determine the therapeutic management and renal prognosis. Treatment, although still based on protocols derived from multiple myeloma and B-cell lymphomas, should be considered even in the absence of classical malignancy, given the nephrotoxic biological activity of monoclonal immunoglobulins [1,5,6].

This article aims to review the main pathophysiological, classificatory, diagnostic, and therapeutic aspects of MGRS, with emphasis on the importance of an interdisciplinary approach between nephrologists and hematologists for the appropriate management of this complex condition.

2 METHODS

This is a narrative review of the literature focusing on the main concepts, pathophysiological mechanisms, diagnostic criteria, and therapeutic approaches related to MGRS.

The research was conducted between January and March 2025, using the PubMed/MEDLINE and SciELO databases. The descriptors used, controlled and uncontrolled, were: "monoclonal gammopathy of renal significance", "MGRS", "monoclonal proteins and kidney", "renal involvement in monoclonal gammopathy", "paraprotein-related kidney disease" and "glomerulopathy and M-protein".

The inclusion criteria included articles published in English and Portuguese in the last 10 years, with priority given to systematic reviews, expert consensus, international clinical guidelines (such as KDIGO and the International Kidney and Monoclonal Gammopathy Research Group), and original studies with practical applicability to nephrology. Studies with redundant data, publications focusing exclusively on hematological malignancies without renal involvement, and case reports with limited scope were excluded.

Content analysis was performed in a narrative manner, with structuring of the findings in pre-defined thematic axes: pathophysiology, classification, diagnosis, and treatment of MGRS.

Methodological limitations: As this is a narrative review, this study does not propose to critically evaluate the methodological quality of the included articles, nor to adopt meta-analysis criteria. The absence of a systematic inclusion strategy can limit reproducibility and increase selection bias. Despite this, the narrative approach allows for the integration, in a broad and contextualized way, of recent advances on the subject, offering relevant subsidies to clinical practice and the formulation of hypotheses for future research.

3 RESULTS

The literature analysis showed that MGRS represents a clinical and histopathological spectrum of renal lesions caused by monoclonal immunoglobulins secreted by hematopoietic clones with low tumor burden, which do not meet diagnostic criteria for multiple myeloma or lymphomas [2,3,7].

The renal manifestations of MGRS are wide and may involve different compartments of the nephron. Glomerulopathies include proliferative glomerulonephritis with monoclonal immunoglobulin (PGNMID) deposits, monoclonal fibrillar glomerulonephritis, and C3 glomerulopathy associated with the presence of paraproteins. The most frequently reported tubulointerstitial lesions are proximal light chain tubulopathy (TPLC) and cast nephropathy.

In addition, organized deposits such as amyloid or microtubules and vascular lesions, such as cryoglobulinaemia vasculitis, are also described in the context of MGRS [4,5,6].

Renal biopsy remains the fundamental diagnostic method, being indispensable for the characterization of the histological lesion, identification of the immune deposit pattern (organized or unorganized) and to establish the causal relationship between the producing clone and nephropathy [2,5]. Immunohistochemistry and immunofluorescence are essential auxiliary techniques in the detection of monoclonality of deposits, while the correlation with hematological tests (electrophoresis, immunofixation, myelogram and serum free light chain) allows the screening of the pathogenic clone [1,6].

Regarding treatment, it was observed that the therapeutic management of MGRS is strongly based on the principles used for hematological malignancies, with adaptations to the low tumor burden profile of these patients. Regimens include the use of proteasome inhibitors, such as bortezomib, anti-CD20 (rituximab) or anti-CD38 (daratumumab) monoclonal antibodies, and alkylating agents in adapted protocols [3,4]. Studies have shown that hematological response — complete or partial — is directly associated with renal response, highlighting the importance of clone-directed therapy [5,7].

The 2021 KDIGO guidelines for glomerular diseases highlight MGRS as a specific diagnostic entity, which must be differentiated from indolent gammopathies and classic malignant dyscrasias. They recommend systematic renal biopsy in the face of findings of unexplained proteinuria or compatible lesions in patients with monoclonal gammopathy, in addition to early referral to the hematological team for evaluation and joint treatment [4].

4 DISCUSSION

The data collected in this review show that MGRS is an autonomous clinicopathologic entity, whose main characteristic is the production of nephrotoxic monoclonal immunoglobulins by hematopoietic clones that are underdiagnosed from an oncological point of view. Despite the low tumor burden, the harmful potential of these proteins on the renal parenchyma is high and often irreversible when the diagnosis is delayed [1,2,5].

Unlike MGUS, which generally presents indolent behavior and does not require immediate intervention, MGRS evolves with clinical aggressiveness from the perspective of nephrology. Early detection of nephrotoxic monoclonal immunoglobulin and rapid identification of the producing clone are crucial steps to contain progressive kidney damage [3,4]. The absence of formal criteria for hematological neoplasia should not postpone the initiation of therapy, since the pathogenic clone, even if small, exerts a continuous deleterious action on the glomeruli and tubules.

One of the greatest clinical challenges lies in the consolidation of specific therapeutic guidelines for MGRS, since most of the adopted conducts derive from extrapolations of the protocols used in classic hematological neoplasms, especially multiple myeloma [4]. However, the available evidence suggests that the hematological response, even if partial, is strongly correlated with stabilization or improvement of renal function, making treatment directed to the clone indispensable [5,7].

Another critical point concerns kidney transplantation in patients with MGRS. Recent studies have shown high rates of recurrence of nephropathy in the graft, especially when the pathogenic clone was not completely suppressed in the pre-transplant period. Thus, it is recommended that transplantation be considered only after obtaining a complete hematological response or, at least, a very good response (VGPR), with close post-transplant monitoring [6].

Therefore, MGRS imposes the need for joint action between nephrologists, hematologists and pathologists. This integrated approach is essential not only for the diagnosis and appropriate management, but also for the design of personalized and cost-effective therapeutic strategies, considering the heterogeneous profile of the disease and the diversity of the histopathological patterns observed.

Thus, the urgency of establishing multicenter prospective studies and clinical trials that validate specific therapeutic regimens for MGRS, define prognostic biomarkers, and structure a universally accepted diagnostic algorithm is reinforced.

5 CONCLUSION

Renal monoclonal gammopathy (MGRS) represents an emerging condition of high clinical relevance, characterized by renal lesions caused by monoclonal immunoglobulins secreted by hematopoietic clones with low tumor burden. Although they do not meet diagnostic criteria for classic hematological neoplasms, these clones demonstrate considerable nephrotoxic potential, with a real risk of progression to end-stage renal disease.

Early recognition of MGRS, supported by renal biopsy and characterization of the pathogenic clone, is decisive for therapeutic success. The introduction of therapies directed at the clone, even in the absence of evident malignancy, is associated with the preservation of renal function and better long-term prognosis. In addition, kidney transplantation should be indicated with caution, ideally after adequate hematological control, in order to reduce the rate of disease recurrence in the graft.

In view of the clinical and histological heterogeneity of MGRS, a multidisciplinary approach and the development of specific guidelines are essential. The consolidation of

prospective studies, controlled clinical trials, and advances in the identification of biomarkers may lead to a more personalized, safe, and effective medicine for patients affected by this still underdiagnosed entity.

MGRS should be seen as a diagnostic and therapeutic urgency in contemporary nephrology practice, requiring active surveillance, interspecialty collaboration, and constant updating in the face of new scientific evidence.

Limitations and Future Prospects: The main limitations observed in the literature include the scarcity of randomized controlled trials, the heterogeneity of diagnostic criteria among centers, and the difficulty in defining standardized prognostic markers. In addition, most therapeutic recommendations are still extrapolated from models used in major hematological malignancies. Future multicenter studies, with well-designed prospective cohorts, are essential to validate conducts, stratify risks, and consolidate specific guidelines for MGRS. The incorporation of new clonal sequencing technologies and renal biomarkers may contribute significantly to the advancement of early diagnosis and personalized therapy.

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