WebLog Journal of Hematology

Mini Review
Published: 09 Mar, 2026

Monoclonal Gammopathy of Renal Significance (MGRS): Bridging the Gap Between Hematology and Nephrology

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Abstract

Monoclonal Gammopathy of Renal Significance (MGRS) is a clinical entity characterized by renal damage caused by monoclonal proteins secreted by clonal plasma or B-cell proliferative disorders, without meeting criteria for overt hematologic malignancies like multiple myeloma or lymphoma. From a hematologist's viewpoint, early identification of the underlying clone is crucial for guiding targeted therapy to preserve renal function.

MGRS lesions are classified into organized deposits (e.g., AL amyloidosis), nonorganized deposits (e.g., monoclonal immunoglobulin deposition disease), and lesions without immune deposits (e.g., thrombotic microangiopathy). Diagnosis requires kidney biopsy with immunofluorescence and electron microscopy. Clone-directed therapies, such as daratumumab-based regimens for plasma cell clones, have improved hematologic and renal outcomes. Renal transplantation is feasible in selected patients with controlled disease.

In conclusion, hematologists play a pivotal role in MGRS management by identifying the pathogenic clone and initiating prompt, targeted treatment to prevent irreversible renal damage. Ongoing research into novel agents and biomarkers promises better prognosis.

Keywords: Monoclonal Gammopathy of Renal Significance – MGRS; Plasma Cell Clone; AL – Amyloidosis; Clone-Directed Therapy

Abbreviations

AH: Amyloid Heavy-chain (amyloidosis), AHL: Amyloid Heavy and Light-chain (amyloidosis), AL: Amyloid Light-chain (amyloidosis), BCMA: B-Cell Maturation Antigen, C3G/C3GP: C3 Glomerulopathy, C3GN: C3 Glomerulonephritis, CKD: Chronic Kidney Disease, eGFR: estimated Glomerular Filtration Rate, EM: Electron Microscopy, ESRD: End-Stage Renal Disease, FLC: Free Light Chain(s), HCDD: Heavy-Chain Deposition Disease, IF: Immunofluorescence, Ig: Immunoglobulin (e.g., IgG, IgA, IgM), IKMG: International Kidney and Monoclonal Gammopathy (Research Group), ITGP: Immunotactoid Glomerulopathy, LCDD: Light-Chain Deposition Disease, LCPT: Light-Chain Proximal Tubulopathy, LHCDD: Light- and Heavy-Chain Deposition Disease, LM: Light Microscopy, MGRS: Monoclonal Gammopathy of Renal Significance, MGUS: Monoclonal Gammopathy of Undetermined Significance, MIDD: Monoclonal Immunoglobulin Deposition Disease, MIg: Monoclonal Immunoglobulin, MPGN: Membranoproliferative Glomerulonephritis, NGS: Next-Generation Sequencing, PGNMID: Proliferative Glomerulonephritis with Monoclonal Immunoglobulin Deposits, sFLC: Serum Free Light Chain, TMA: Thrombotic Microangiopathy

Introduction

Monoclonal gammopathy of renal significance (MGRS) was first defined in 2012 to describe renal disorders caused by monoclonal immunoglobulins (MIgs) produced by small B-cell or plasma cell clones that do not fulfill criteria for symptomatic multiple myeloma, Waldenström macroglobulinemia, or lymphoma [1]. This term distinguishes MGRS from Monoclonal Gammopathy of Undetermined Significance (MGUS), which lacks organ damage, and emphasizes the need for treatment despite low tumor burden [2]. From a hematologist's perspective, MGRS represents a paradigm where the pathogenicity stems not from clonal mass but from the toxic properties of the secreted MIg, necessitating a multidisciplinary approach with nephrologists.

The prevalence of MGRS among patients with monoclonal gammopathies is estimated at 0.32% in those over 50 years, constituting about 10% of MGUS cases [3]. Kidney involvement predominates due to the kidneys' role in filtering and processing MIgs, leading to diverse lesions governed by MIg

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Received Date: *12 Feb 2026*
Accepted Date: *07 Mar 2026*
Published Date: *09 Mar 2026*

Citation:
Embaby A. Monoclonal Gammopathy of Renal Significance (MGRS): Bridging the Gap Between Hematology and Nephrology. WebLog J Hematol. wjh.2026.c0902. https://doi.org/10.5281/zenodo.19238940

molecular features like charge, hydrophobicity, and glycosylation [4].

Clinical Presentation and Diagnosis

MGRS often presents with insidious renal impairment, proteinuria, hematuria, or hypertension, sometimes discovered incidentally [5]. Extrarenal manifestations, such as hepatomegaly or elevated liver enzymes, may hint at systemic involvement, Thus, hematologists must suspect MGRS in patients with unexplained renal disease and monoclonal gammopathy [6]. Diagnosis requires a kidney biopsy, essential for confirming MIg-related damage [7]. Histologic analysis includes light microscopy, Immunofluorescence (IF) on frozen and paraffin tissue (with pronase digestion for masked deposits), and Electron Microscopy (EM) to assess deposit organization [8]. Paraffin IF is particularly useful for detecting monotypic deposits in AL amyloidosis or Light Chain Proximal Tubulopathy (LCPT) [9]. Hematologic evaluation is crucial to identify the underlying clone. Serum and urine protein electrophoresis with immunofixation, serum Free Light Chain (FLC) assay, and bone marrow aspiration/biopsy with flow cytometry, cytogenetics, and NGS are standard [10].

Approximately 80-100% of MGRS cases reveal a clonal disorder, most commonly plasma cell (e.g., in AL amyloidosis) or B-cell (e.g., in cryoglobulinemia) [11]. In the absence of detectable serum/urine MIg (10-20% of cases), advanced techniques like mass spectrometry or RNA-based immunoglobulin range sequencing may be employed [12].

Classification of MGRS Lesions

MGRS renal lesions are classified by the International Kidney and Monoclonal Gammopathy (IKMG) Research Group into three groups based on deposit composition and EM ultrastructure [13], that guides therapy by linking pathology to the clone type.

1. Organized Deposits: These include fibrillar, microtubular, or crystalline structures:

• AL/AH/AHL Amyloidosis: Randomly oriented 8-12 nm fibrils staining Congo red-positive. Predominantly lambda LCs (75%), often from Vλ6 subgroup. Glomerular, vascular, and interstitial deposits cause proteinuria and progressive CKD [14].

• Immunotactoid Glomerulopathy (ITGP): Microtubules >30 nm in diameter, typically monotypic IgG kappa, leading to mesangial proliferative glomerulonephritis [15].

• Cryoglobulinemic Glomerulonephritis: Type I (monoclonal) or II (mixed) cryoglobulins form microtubular deposits, causing Membranoproliferative Glomerulonephritis (MPGN) with vasculitis [16].

• Crystalline Lesions: Include LCPT (Fanconi syndrome with kappa LC crystals in proximal tubules), crystal-storing histiocytosis (histiocytic crystals), and crystalglobulinemia (vascular crystals causing thrombosis) [17].

2. Nonorganized Deposits: Amorphous "powder-like" deposits on EM:

• Monoclonal Ig Deposition Disease (MIDD): Includes LCDD (LC only, mostly kappa Vκ4), HCDD (heavy chain, often gamma with CH1 deletion), and LHCDD. Deposits along basement membranes cause nodular sclerosis and tubular atrophy [18].

• Proliferative Glomerulonephritis with Monoclonal Ig Deposits (PGNMID): Mesangial/endocapillary proliferation with monotypic IgG3 deposits, often without detectable circulating MIg [19].

3. Lesions Without MIg Deposits:

• C3 Glomerulopathy (C3GP): C3-dominant deposits due to MIg-induced alternative pathway dysregulation, including C3GN and dense deposit disease [20].

• Thrombotic Microangiopathy (TMA): Endothelial injury from complement activation or direct MIg toxicity, without deposits [21].

Treatment Strategies

Treatment aims to eradicate the pathogenic clone, halt MIg production, and preserve renal function. The corner stone is clone-directed therapy, tailored to clone type and renal status [22]. For plasma cell clones (e.g., AL amyloidosis, MIDD, PGNMID), frontline regimens include daratumumab, cyclophosphamide, bortezomib, and dexamethasone (Dara-VCD), achieving deep responses in >80% of cases [23]. In high-risk AL amyloidosis with t(11;14), BCL-2 inhibitors like venetoclax is promising [24]. For relapsed disease, anti-BCMA therapies like teclistamab or CAR-T cells show efficacy [25]. B-cell clones (e.g., in cryoglobulinemia or C3GP) respond to rituximab-based regimens; Bruton tyrosine kinase inhibitors are useful in Waldenström-associated cases [26]. Supportive care includes renin-angiotensin system blockers for proteinuria, dialysis for End-Stage Renal Disease (ESRD), and anticoagulation for nephrotic syndrome [27]. Early intervention before severe CKD (eGFR <30 mL/min) improves outcomes; delayed diagnosis correlates with progression to ESRD [28].

Response Assessment

Validated criteria exist for AL amyloidosis: hematologic response (e.g., very good partial response: dFLC <40 mg/L) correlates with renal response (≥30% proteinuria reduction) [29]. For other MGRS, uniform criteria are lacking; response is assessed by FLC reduction, proteinuria decrease, and eGFR stabilization [30]. Novel biomarkers like mass spectrometry for minimal residual disease detection may refine monitoring [31].

Renal Transplantation

Historically underutilized due to recurrence risk, renal transplantation is now feasible in MGRS patients achieving sustained hematologic remission [32]. Recurrence rates vary high in untreated PGNMID (50-60%), low in AL amyloidosis post-autologous stem cell transplant (<10%) [33]. Pretransplant clone control and post-transplant monitoring are essential [34].

Future Directions

Emerging therapies include next-generation anti-CD38 antibodies and bispecifics for refractory cases [35]. Biomarkers like DNAJB9 for fibrillary GN and complement genetics for C3GP may enhance diagnosis [36]. Collaborative registries will clarify rare subtypes and optimize guidelines.

Conclusion

From a hematologist's perspective, MGRS underscores the importance of recognizing small clones causing significant organ damage. Prompt diagnosis via biopsy and hematologic workup, followed by clone-targeted therapy, is key to improving renal and overall survival. Multidisciplinary collaboration and novel agents offer hope for better management, emphasizing that in MGRS, the clone's impact far exceeds its size.

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