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Christian Sebesta *

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Review Article

Novel and Personalized Therapy for Monoclonal Gammopathy of Renal Significance

Christian Sebesta [1,2]*, Helena Bozic[3], Christian G Sebesta[2], Marie Christine Sebesta[2], Boris Bozic[4]

[1]2nd Medical Department, Hematology and Oncology, Klinik Donaustadt, 1220 Vienna, Austria.

[2]Danube Science, 1220 Vienna, Austria.

[3]Center for Pathophysiology, Infectiology and Immunology, Institute of Immunology, Medical University of Vienna, Austria.

[4]Medical Clinic, Hematology and Oncology, See-Spital Horgen, 8810 Horgen, Switzerland.

***Corresponding Author:** Christian Sebesta, 2nd Medical Department, Hematology and Oncology, Klinik Donaustadt, 1220 Vienna, Austria.

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Abstract

Monoclonal gammopathy of renal significance (MGRS) refers to renal diseases caused by a monoclonal protein (M protein) secreted by a small plasma cell clone or other B-cell clones in patients who do not meet the diagnostic criteria for multiple myeloma or other B-cell malignancies. MGRS results from the deposition of composite monoclonal immunoglobulin (Ig) and light or heavy chain (LC or HC) fragments of varying sizes produced by plasma cells or plasmoblasts that proliferate clonally, possibly under the influence of T-helper lymphocytes. The diagnosis of MGRS involves four steps: (1) identifying the underlying monoclonal protein in serum and urine, (2) determining the clonal B-cell population responsible for secreting the monoclonal protein, (3) assessing any extrarenal manifestations of the clonal B-cell population, and (4) performing a renal biopsy to identify the pattern of renal parenchymal damage and detect monoclonal protein. Treatment for MGRS is based on targeting the causative B-cell clone. The goal of treatment is to preserve or improve organ function by targeting the B-cell or plasma cell clone responsible for M-protein production and organ damage. Several substances are available for treatment, including proven options such as bortezomib, cyclophosphamide, and pomalidomide, as well as newly developed substances like CD38 antibodies (daratumumab, isatuximab), monoclonal antibodies targeting BCMA, BCL-2 inhibitors (venetoclax), and chimeric antigen receptor (CAR) T-cells.

Keywords: monoclonal gammopathy of renal significance; renal biopsy; bortezomib; pomalidomide; daratumumab; isatuximab; monoclonal antibodies targeting bcma; venetoclax; chimeric antigen receptor (car) t-cells

Introduction

Monoclonal gammopathy of renal significance (MGRS) encompasses all kidney diseases caused by a nephrotoxic monoclonal immunoglobulin (M-protein) produced by a small, often indolent plasma cell or B-cell clone in patients who do not fulfill the diagnostic criteria for overt multiple myeloma (MM), Waldenström's macroglobulinemia (WM), chronic lymphocytic leukemia (CLL), or lymphoma [1]. According to the updated consensus of the International Kidney and Monoclonal Gammopathy Research Group (IKMG), MGRS includes not only monoclonal gammopathy of undetermined significance (MGUS) but also other premalignant or early clonal disorders such as smoldering multiple myeloma (SMM), smoldering Waldenström macroglobulinemia (SWM), and monoclonal B-cell lymphocytosis, provided that the secreted monoclonal protein is directly responsible for renal injury [2]. Once the hematologic disorder progresses to MM, WM, advanced CLL, or malignant lymphoma, the condition is no longer classified as MGRS and treatment follows disease-specific oncologic protocols. Kidney involvement associated with monoclonal gammopathy is increasingly recognized in clinical practice. The spectrum of MGRS-associated nephropathies continues to expand and includes glomerular, tubulointerstitial, and vascular lesions, occurring either in isolation or combination. Accurate diagnosis requires establishing (i) the presence of a monoclonal gammopathy, (ii) the underlying pathogenic clone, and (iii) the specific pattern of renal injury [3]. Recent epidemiologic data indicate that patients with MGRS have a significantly higher risk of progression to MM compared with MGUS: Steiner et al. reported a median progression time of 18.8 years, with a 10% progression risk within the first year in MGRS versus 1% in MGUS [4].

From a hematologic perspective, MGRS due to a plasma cell clone is typically characterized by <10% bone marrow plasma cells, <3 g/dL M-protein, and absence of myeloma-defining events, despite the presence of a monoclonal protein biologically capable of causing organ damage-most prominently renal injury [5].

The aim of this review is to provide a comprehensive, clinically oriented overview of monoclonal gammopathy of renal significance, focusing on:

- the diagnostic approach including laboratory evaluation and biopsy based classification,
- the histopathologic spectrum of MGRS-associated renal lesions, and
- current and emerging clone directed therapeutic strategies.

Particular emphasis is placed on integrating nephrologic and hematologic perspectives to support timely recognition and optimal management of this increasingly relevant clinical entity.

2. Pathogenesis of MGRS

MGRS results from the deposition of monoclonal immunoglobulins (Ig) and light or heavy chain (LC or HC) fragments of various sizes released by plasma cells or plasmoblasts that proliferate clonally, possibly under the influence of helper T lymphocytes [5]. Immunoglobulins consist of two heavy (H) chains and two light (L) chains, where the L chain can be either κ (kappa) or λ (lambda). Each component chain contains an NH2-terminal "variable (V) IgSF" domain and one or more COOH-terminal "constant" (C) IgSF domains, each consisting of two β-sheets connected by a disulfide bridge between conserved cysteine residues [6]. Similar to HC, the two LC in a single Ig are identical. Mammals have two types of light chains, λ (lambda) and κ (kappa), with each Ig containing only one type. Each LC has a constant domain followed by a variable domain, approximately 215 amino acids in length [7]. About 30% of nephrotoxic free light chains (FLCs) secreted by plasma cell dyscrasias cause glomerular disease. Recent experiments have shown that specific monoclonal FLCs can cause glomerular lesions, including both light chain-associated (AL) amyloidosis and light chain deposition disease (LCDD) in animal models [8, 9, 10]. A study by Tang et al. revealed that most patients with MGRS had amyloidosis (n = 25), followed by cryoglobulinemic glomerulonephritis (cryo-GN, n = 7), proliferative glomerulonephritis with monoclonal IgG deposition (PGNMID, n = 5), and monoclonal immunoglobulin deposition disease (MIDD, n = 3) [12]. Table 1 presents the classification of renal lesions associated with monoclonal gammopathy of renal significance.

Pathogenesis of AL Amyloidosis

AL amyloidosis is an indolent plasma cell disorder characterized by the misfolding of free light chains (FLC) and the deposition of amyloid fibrils in various tissues [13]. The plasma cell clone in AL amyloidosis is typically small and indolent, secreting light chains in 75–80% of cases, and exhibits phenotypic and copy number alterations similar to those seen in multiple myeloma (MM) clones [18]. In AL amyloidosis, amyloid fibrils derived from monoclonal immunoglobulin light chains accumulate in multiple organs such as the heart, kidneys, liver, gastrointestinal tract, and peripheral nerves, causing diverse clinical manifestations [14,15]. The deposition of amyloid fibrils disrupts tissue architecture and cell membranes, and increased oxidative stress and proteotoxicity arise due to the action of amyloid oligomers [19,20]. Studies on immunoglobulin light chains suggest that specific IgL germline gene usage and point mutations in the IgL locus may predict organ tropism and fibril-forming propensity in AL amyloidosis [15]. Bochtler et al. first reported in 2015 that t(11;14) is associated with poorer outcomes in patients receiving bortezomib-based regimens [16]. Patients with t(11;14) also benefit from high dose melphalan chemotherapy followed by autologous stem cell transplantation (ASCT), with significantly higher response rates, better hematologic event-free survival, and a tendency for improved overall survival. Multivariate analysis identified t(11;14) as a favorable prognostic factor for hematologic event-free survival in patients treated with HDM+ASCT [17].

Histologic subtypes of renal involvement in AL amyloidosis have important prognostic and therapeutic implications [124].

Pathogenesis of Monoclonal Fibrillary Glomerulonephritis

Fibrillary glomerulonephritis (FGN) is a rare glomerular disease first described by Rosenmann and Eliakim in 1977 [21]. It is characterized by the accumulation of randomly arranged, straight fibrils in the glomeruli, which have a thickness of 12-24 nm under electron microscopy [22]. Most cases of FGN exhibit mesangial expansion, with or without glomerular basement membrane (GBM) duplication, and are less frequently associated with endocapillary hypercellularity or crescentic glomerulonephritis. Immunofluorescence typically shows a "smeared" granular staining for immunoglobulin G (IgG), which may be polyclonal, oligoclonal, or monoclonal, along with complement deposition (predominantly C3, and occasionally C1q) [23]. Studies indicate that approximately 10% of FGN patients have a monoclonal gammopathy, and it is now standard practice to screen these patients for monoclonal gammopathies [24]. DNAJB9, a heat shock protein found in the endoplasmic reticulum and involved in the endoplasmic reticulum stress/unfolded protein response (UPR) pathway, has been detected in glomeruli in renal biopsy samples using liquid chromatography and mass spectrometry [25]. However, local activation of the UPR pathway does not seem to drive the pathogenesis of FGN. One proposed mechanism is that increased circulating levels of DNAJB9, along with an autoantibody response in the glomeruli, results in an excess of DNAJB9 [26].

Pathogenesis of Immunotactoid Glomerulonephritis

Immunotactoid glomerulopathy (ITG) is a rare form of glomerulonephritis associated with proteinuria, hematuria, and renal insufficiency. Electron microscopy reveals characteristic microtubular deposits with diameters ranging from 14-60 nm, often arranged in parallel and predominantly located outside the lamina densa of the glomerular basement membrane. Immunofluorescence typically shows IgG-dominant staining, which in 67% of cases is restricted to light chains and IgG subclasses, indicating a monoclonal composition. Monoclonal ITG is more frequently associated with lymphoma (53% vs. 11%), multiple myeloma (8% vs. 0%), and monoclonal gammopathy (22% vs. 16%) compared to polyclonal ITG [27].

Pathogenesis of Cryoglobulinemic Glomerulonephritis

Cryoglobulinemic glomerulonephritis is characterized by the intraglomerular deposition of immune complexes, complement activation, leukocyte influx, and glomerular remodeling [28]. Brouet et al. classified cryoglobulins into three subtypes based on immunofixation: Type I consists solely of monoclonal immunoglobulins (paraproteins); Type II includes both monoclonal and polyclonal immunoglobulins; and Type III contains only polyclonal immunoglobulins. Types II and III are often referred to as mixed cryoglobulinemia due to their overlapping clinical presentations and pathophysiology [29]. Type II cryoglobulinemia represents the most common subtype of cryoglobulin-associated disorders, accounting for approximately 50–65% of all cases [30]. Type III cryoglobulins, which contain mixed polyclonal IgM and IgG components, account for 25-40% of cases and are often associated with autoimmune diseases or infections such as hepatitis C [31]. Renal involvement occurs in about 29% of patients with cryoglobulinemia, being most common in patients with Type II cryoglobulins (approximately 84%) and rare in those with Type I (about 4%) and Type III cryoglobulins (about 11%) [32]. Aberrant B-cell function and lymphoproliferation are key factors associated with cryoglobulin

production, especially in patients infected with the hepatitis C virus. Hepatitis C virus enters B cells via the CD81 receptor, which is present on both hepatocytes and B cells, leading to infection and subsequent dysfunction and proliferation of B cells, which release mixed cryoglobulins into the circulation [33].

Pathogenesis of Light Chain Proximal Tubulopathy

Light chain proximal tubulopathy (LCPT) is characterized by the cytoplasmic accumulation of monoclonal light chains within proximal tubule cells. LCPT is most commonly caused by light chains of the kappa-I (κI) subgroup, which are inadequately degraded by lysosomes. These abnormal, truncated kappa light chains fail to bind to Tamm-Horsfall glycoprotein, which is why light chain cast nephropathy is not typically associated with this condition.[34] A hallmark of LCPT is the crystallization of κ-light chains within the proximal tubules, and this condition is associated with Fanconi syndrome in approximately 40% of patients. [35]. LCPT without crystals can be linked to either κ- or λ-light chain accumulation. The excessive light chains absorbed into the cytoplasm of proximal tubule cells lead to the formation of crystalline structures that can be identified via immunofixation and electron microscopy. These crystals are electron-dense, typically exhibiting a rhomboid, square, or rectangular shape, and can be found within the lysosomes of proximal tubule cells [36]. Patients with LCPT generally present with a subacute decline in renal function and low-grade proteinuria. The renal impairment can be mild and progress slowly over the course of several years, though renal failure is also possible.[37]

Pathogenesis of Crystal-Storing Histiocytosis

Crystal-storing histiocytosis is characterized histologically by intracellular crystalline inclusions within histiocytes, which accumulate and affect various organs throughout the body. It is commonly associated with lymphoproliferative disorders, particularly those with plasmacytic differentiation, including multiple myeloma, lymphoplasmacytic lymphoma, marginal zone lymphoma with plasmacytic differentiation, and monoclonal gammopathy of undetermined significance. [38]

Pathogenesis of Monoclonal Immunoglobulin Deposition Disease (MIDD)

Monoclonal immunoglobulin deposition disease (MIDD) encompasses a group of disorders characterized by the linear deposition of monoclonal light chains (LCDD), heavy chains (HCDD), or both (LHCDD) along basement membranes, most commonly in the kidney. Unlike AL amyloidosis, MIDD deposits are non-fibrillar and Congo-red negative, but share the same underlying mechanism of monoclonal gammopathy [122]. Renal involvement typically manifests with proteinuria, often in the nephrotic range, and progressive renal insufficiency. Histologically, thickening of glomerular and tubular basement membranes is observed, with nodular glomerulosclerosis resembling diabetic nephropathy. Diagnosis is confirmed by immunofluorescence and electron microscopy, revealing the nature and localization of the deposits. Effective treatment requires prompt clone-directed therapy. Bortezomib-based regimens have shown excellent hematologic and renal responses [123]. Autologous stem cell transplantation (ASCT) can be useful as a therapeutic strategy in MIDD.

C3-Glomerulopathy with Monoclonal Gammopathy

C3 glomerulopathy (C3G) is a rare and heterogeneous group of glomerular diseases characterized by predominant C3 deposition in the glomeruli without significant immunoglobulin deposits. It includes dense deposit disease (DDD) and C3 glomerulonephritis (C3GN). In the context of MGRS, C3G can result from a monoclonal gammopathy-induced dysregulation of the alternative complement pathway. Monoclonal immunoglobulins may act as autoantibodies against complement regulatory proteins such as factor H or factor I, or serve as nephritic factors stabilizing C3 convertase. Diagnosis requires renal biopsy with immunofluorescence and electron microscopy. Complement studies and serum monoclonal protein evaluation are essential. Evidence of a pathogenic monoclonal clone should prompt clone-directed therapy, although data on optimal management remain limited [47].

Monoclonal immunoglobulin deposits			
Fibrillar	Microscopic patterns	Monoclonal Protein	Organ damage
AL amyloidosis	Congo red positive fibrils (7-12 nm)	FLC (λ > κ)	affects heart, kidney,liver
Monoclonal fibrillary GN	Congo red negative fibrils (10-30 nm)	IgG, C3, κ/λ deposits	Kidney
Microtubular			
Immunotactoid GN	Coarse microtubules (17-52 nm)	mesangial IgG, C3, parallel arrays	Kidney
Crioglobulinemic GN	not organized deposits	includes IgM/IgG, C3, sometimes crystalline	Kidney
Crystalline or inclusion-forming lessions			
Light chain proximal tubulopathy	cristalline (κ, Fanconi non-crystalline (λ, rare	LC inclusions within tubular epithelium	Kidney
Crystal storing hystiocytosis	histiocytes with LC crystals	LC crystalloid inclusions within macrophages/histiocytes BM, LN, lungs	Kidney, lung

Not organized			
Monoclonal immunoglobulin Deposition disease (MIDD)	Light or heavy chains distributed along GBM and TBM IgG1	LCDD: mesangial and/or glomerular basement membrane monoclonal LC deposits HCDD: k and l negative, staining for 1 of the immunoglobulins (most commonly IgG or IgM)	Kidney, Liver, Heart
Proliferative GN with monoclonal deposits (PGNMID)	IgG/LC deposits with proliferative GN pattern	monoclonal immunoglobulin or, more rarely, monoclonal LC deposits	Kidney
Complement-mediated (without direct Ig deposits)			
C3 glomerulopathy	Monoclonal gammopathy detectable in 60-80% of individuals >50 years with C3 glomerulonephritis	Granular, C3-dominant deposits	Kidney
Thrombotic microangiopathy (TMA) provisional			
POEMS	provisional		
Monoclonal immunoglobulin deposits			
Fibrillar	Microscopic patterns	Monoclonal Protein	Organ damage
AL amyloidosis	Congo red positive Fibrils (7-12 nm)	FLC (λ > κ)	affects heart, kidney, liver
Monoclonal fibrillary GN	Congo red negative Fibrils (10-30 nm)	IgG, C3, κ/λ deposits	Kidney
Microtubular			
Immunotactoid GN	Coarse microtubules (17-52 nm)	Mesangial IgG, C3, parallel arrays	Kidney
Crioglobulinemic GN	Not organized deposits	includes IgM/IgG, C3, sometimes crystalline	Kidney
Crystalline or inclusion-forming lessions			
Light chain proximal tubulopathy	Cristalline (κ, Fanconi non-crystalline (λ, rare	LC inclusions within tubular epithelium	Kidney
Crystal storing hystiocytos	Histiocytes with LC crystals	LC crystalloid inclusions within macrophages/histiocytes BM, LN, lungs	Kidney, lung

Table 1: Classification of monoclonal gammopathy of renal significance-associated renal lesions

Abbreviations: BM, bone marrow; GBM, glomerular base membrane; LN, lymph node; TBM, tubular base membrane

* Adapted from [2]

3. Diagnostics of MGRS

Due to the differences in clinical presentation, prognosis, and therapeutic strategies, it is essential to distinguish MGUS-associated findings from renal diseases that are not caused by monoclonal immunoglobulins [51]. The diagnostic work-up of suspected MGRS consists of four core steps:

- Detection of the monoclonal protein in serum and urine,
- Identification of the underlying clonal B-cell or plasma cell population,
- Assessment of extrarenal manifestations related to the clone, and
- Renal biopsy to determine the pattern of parenchymal injury and confirm monoclonal immunoglobulin deposition [49].

Several laboratory findings increase the pretest probability of MGRS, including urinary protein excretion >1.5 g/day, an abnormal serum free light chain (FLC) ratio, and microscopic hematuria. In patients with monoclonal gammopathy and these abnormalities or in those with otherwise unexplained acute or progressive renal dysfunction a renal biopsy should be performed early [50]. Despite this, renal biopsy remains underused: in one multicenter study, only 12.9% of patients with monoclonal gammopathy and renal impairment underwent kidney biopsy, yet over 40% of those biopsied had lesions unrelated to their monoclonal gammopathy, with amyloid nephropathy being the most common [52].

Given the prognostic impact of renal function and the low complication rate of native kidney biopsy, this procedure is considered safe and essential to establish a correct diagnosis and should be strongly recommended in all patients with suspected MGRS [52]. In selected high-risk cases, a transjugular renal biopsy allows safe tissue acquisition when percutaneous biopsy poses unacceptable risk [53]. Detection of monoclonal immunoglobulin deposits in renal tissue confirms the presence of a pathogenic B-cell or plasma cell clone. Therefore, once a monoclonal deposit is identified, further efforts must focus on precise immunophenotypic and molecular characterization of the clone, as this directly determines treatment strategy [54]. Biochemical detection of monoclonal proteins requires a combination of serum and urine studies. Serum protein electrophoresis (SPE), with a detection limit of 500-2000 mg/L, lacks sufficient sensitivity—especially for free light chains, which have short plasma half-lives. In contrast, the serum free light chain assay (sFLC) achieves sensitivity below 5 mg/L, making it indispensable for detecting subtle abnormalities in free light chain synthesis [57]. However, SPE should be complemented by serum and urine immunofixation, which are more sensitive for identifying intact monoclonal immunoglobulins and allow determination of the isotype even when SPE is inconclusive [55]. Serum immunofixation is roughly ten times more sensitive than SPE, yet urine immunofixation or sFLC measurement is often required to detect low level monoclonal proteins [56]. Although urine electrophoresis is the least sensitive assay for detecting monoclonal gammopathy—since only free light chains are filtered through the glomerulus—its diagnostic value remains high because it reliably distinguishes cast nephropathy (dominant light chains) from AL amyloidosis/MIDD (selective albuminuria). It also provides quantitative information on total and albumin protein excretion, which assists in diagnosis, prognostication, and response assessment [58]. Once a monoclonal protein has been identified, clone characterization becomes essential. Plasma cell derived clones (typically producing κ or λ light chains) require myeloma based treatment algorithms, whereas lymphoplasmacytic or B-cell clones (e.g., IgM-producing clones) often demand anti-CD20 based therapy or lymphoma directed regimens [59]. Despite growing recognition of MGRS as a distinct entity, no universally accepted renal response criteria exist across its histologic subtypes. This lack of standardization limits the comparability of clinical studies and complicates assessment of treatment efficacy [2,54]. In contrast, AL amyloidosis benefits from well validated and broadly accepted organ response criteria, a model underscoring the need for uniform, subtype specific renal endpoints in MGRS.

4. Therapy of MGRS

The treatment of MGRS is aimed at targeting the causative B-cell or plasma cell clone. The therapeutic management of monoclonal gammopathy of renal significance (MGRS) requires an integrated and clone-directed approach that combines insights from hematology, nephrology, and histopathology. Rather than listing available agents in isolation, therapy should be structured according to the underlying pathogenesis, histological lesion, and type of monoclonal clone (plasma cell vs. B-cell origin), while taking into account the extent of renal and extrarenal involvement. MGRS comprises a heterogeneous group of renal diseases caused by nephrotoxic monoclonal immunoglobulins or their fragments secreted by small, otherwise non-malignant B-cell or plasma cell clones. The pathological spectrum includes amyloid forming disorders (e.g., AL amyloidosis), non-fibrillar immunoglobulin deposition diseases (e.g., LCDD, HCDD), and complement-mediated glomerulopathies (e.g., C3 glomerulopathy), among others. These entities are unified by the presence of a monoclonal protein that leads to organ damage despite the absence of overt hematologic malignancy [2,5]. Diagnostic evaluation should aim to identify the responsible clone through serum and urine protein electrophoresis, immunofixation, serum free light chain analysis, and bone marrow biopsy. Renal biopsy is essential to confirm the lesion and detect monoclonal deposits via immunofluorescence and electron microscopy. Clone characterization is critical for treatment selection: plasma cell derived lesions (e.g., AL, LCDD) are treated with myeloma type regimens, whereas B-cell driven disorders (e.g., PGNMID, immunotactoid GN) often respond to rituximab based therapies [2,3,54]. The therapeutic goal is to preserve renal function and prevent systemic progression by achieving deep and durable hematologic responses. Agents must be selected based on efficacy and tolerability in patients with renal impairment. Proteasome inhibitors (e.g., bortezomib, ixazomib), monoclonal antibodies (e.g., daratumumab, rituximab), and immunomodulatory drugs (e.g., lenalidomide, pomalidomide) are central to most regimens. Novel agents such as venetoclax, teclistamab, and CAR-T cells are increasingly relevant, especially in relapsed or refractory disease and in genetically defined subgroups (e.g., t (11;14)) [69,70,109]. Importantly, treatment response should be monitored using both hematologic and organ-specific parameters, as hematologic remission often precedes renal improvement. The lack of uniform renal response criteria across MGRS subtypes remains a major limitation in clinical evaluation and trial design [2,54].

By embedding therapeutic decisions in a pathophysiological and diagnostic framework, clinicians can better tailor interventions to disease biology and improve long term outcomes in MGRS.

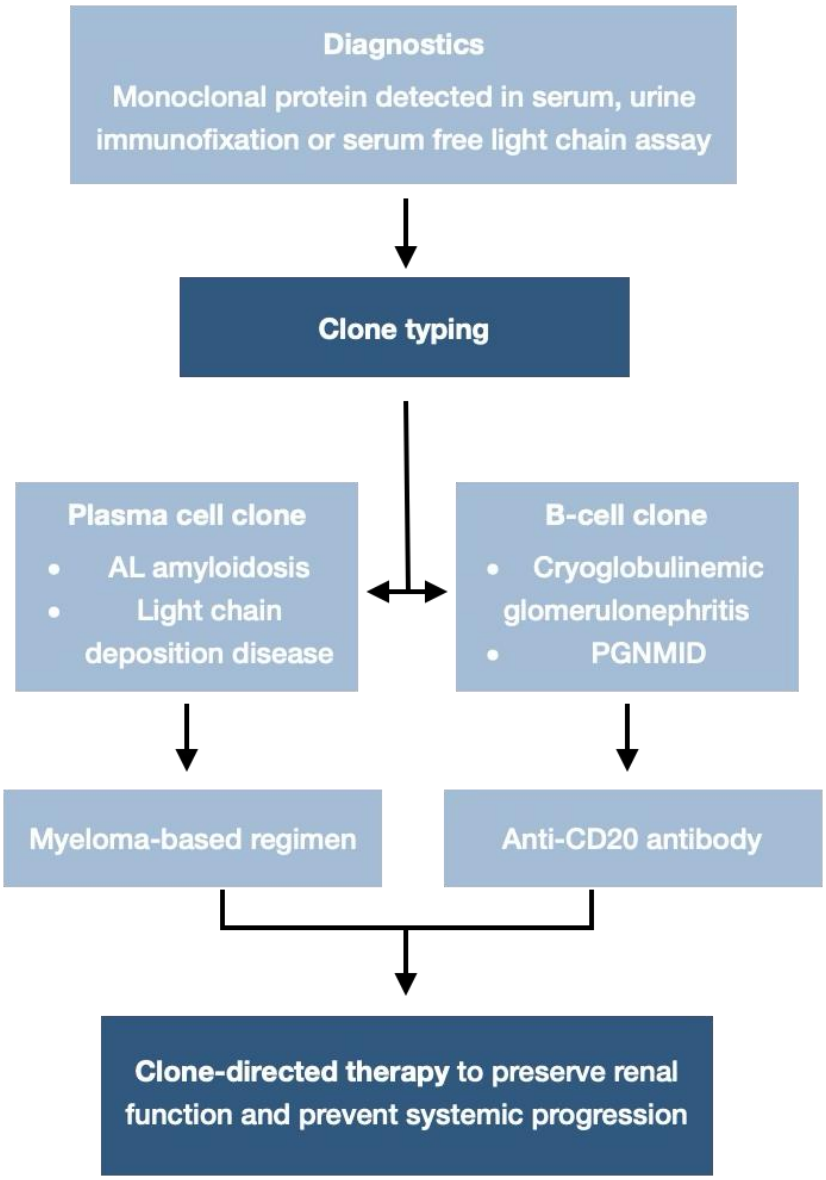

Figure 1: Proposed workflow. Diagnostic and therapeutic algorithm in MGRS, stratified by by clonal origin and renal lesion type. [2]

4.1. Treatment of Newly Diagnosed AL Amyloidosis

The primary therapeutic objective in newly diagnosed AL amyloidosis is the rapid suppression of amyloidogenic free light chains to prevent irreversible organ damage. Treatment selection depends on transplant eligibility, organ involvement and patient frailty. In transplant eligible patients, high dose melphalan followed by autologous stem cell transplantation (HDM/ASCT) remains the standard of care. When appropriately selected, this approach leads to high hematologic complete response (CR) rates and long-term survival benefit. However, treatment-related mortality remains significant in patients with cardiac involvement and poor performance status, underscoring the need for careful pre-transplant risk stratification [67,68]. For transplant ineligible patients, the combination of daratumumab, cyclophosphamide, bortezomib, and dexamethasone (Dara-CyBorD) has become the frontline standard. The phase III ANDROMEDA trial demonstrated superior hematologic and organ response rates with Dara-CyBorD compared to CyBorD alone. Hematologic CR was achieved in 53% of patients, and 79% achieved a very good partial response (VGPR) or better [72]. Daratumumab is safe and effective even in patients with severe renal impairment or dialysis dependency [97]. Bortezomib, given subcutaneously once weekly, is favored for its efficacy and tolerability in renal dysfunction. Cyclophosphamide and dexamethasone contribute synergistically with minimal additional toxicity.[74]

4.2. Treatment of Relapsed or Refractory AL Amyloidosis

In relapsed or refractory AL amyloidosis, treatment choice is guided by prior therapy, duration and depth of response, cytogenetic features, and organ reserve. Pomalidomide, a third-generation IMiD, has demonstrated efficacy in patients previously exposed to proteasome inhibitors. In a European multicenter retrospective study, pomalidomide with dexamethasone achieved a hematologic response in 55–65% of patients, with median progression-free survival (PFS) of up to 37 months among responders [93]. Ixazomib, an oral proteasome inhibitor, offers an attractive alternative for frail patients. In the TOURMALINE-AL1 trial, ixazomib/dexamethasone showed comparable hematologic response rates to physician's choice (53% vs. 51%) but was associated with longer organ PFS and improved tolerability [87]. For patients with the t(11;14) translocation, venetoclax - a selective BCL-2 inhibitor - has shown

outstanding efficacy. A retrospective cohort study reported hematologic response rates of 81%, with deep remissions (VGPR or better in 78%) and organ response in 83% of evaluable patients [109]. In heavily pretreated or refractory disease, emerging immunotherapies show promising potential. Teclistamab, a bispecific antibody targeting BCMA, achieved 100% VGPR or better in a small cohort of AL amyloidosis patients [69]. Anti-BCMA CAR-T cells have also demonstrated remarkable hematologic responses and organ improvement in selected patients, with acceptable toxicity profiles [70]. While AL amyloidosis is typically caused by a small plasma cell clone secreting free light chains, a subset of cases arises from a B-cell or lymphoplasmacytic clone producing intact monoclonal IgM or IgG. This clonal origin has important clinical and therapeutic implications. Plasma cell-associated AL amyloidosis accounts for the vast majority of cases and responds well to antimyeloma regimens such as bortezomib based combinations, daratumumab, or high dose melphalan with autologous stem cell transplantation [65,72]. In contrast, B-cell driven AL amyloidosis, which constitutes approximately 5-7% of cases, is often associated with lymphoplasmacytic lymphoma or other indolent B-cell neoplasms. These patients typically produce monoclonal IgM and require treatment with anti-CD20-based regimens such as rituximab plus bendamustine or BTK inhibitors in selected cases [107]. Given the overlapping histologic features but divergent therapeutic approaches, accurate clone identification via bone marrow biopsy and immunophenotyping is critical prior to initiating therapy.

4.3. Novel Agents in the Therapy of AL Amyloidosis

Proteasome Inhibitors

Bortezomib

Bortezomib is effective and well tolerated by patients with impaired renal function, including those requiring dialysis [75]. It is administered as a single agent or in combination with dexamethasone and alkylating agents (e.g., melphalan, cyclophosphamide) [76]. For AL amyloidosis, subcutaneous bortezomib once weekly, with a risk-adapted dosage, is typically preferred [77]. Bortezomib is suspected of causing cardiotoxicity, so it should be used with caution, especially in the presence of cardiac involvement [78]. The pharmacokinetics of bortezomib are not affected by the degree of renal dysfunction, as its primary metabolic pathway is oxidative deboronation via hepatic cytochrome P450 enzymes [79]. No dose adjustment is necessary in patients with impaired renal function. Bortezomib is not recommended for patients with peripheral polyneuropathy [80].

Carfilzomib

Carfilzomib is a tetrapeptide epoxyketone proteasome inhibitor that irreversibly binds with greater affinity to the 5-proteasome subunit and the LMP7 subunit of the immunoproteasome compared to bortezomib [83]. According to available pharmacokinetic data, no initial dose adjustment is required for patients with mild, moderate, or severe renal impairment, or for those undergoing chronic dialysis therapy [84]. In AL amyloidosis, carfilzomib should be used with caution due to documented cardiac, pulmonary, and renal toxicities, especially in patients with multiple organ involvement. However, in a small group of patients without cardiac deposits and with peripheral neuropathy, carfilzomib was well tolerated and highly effective [85].

Ixazomib

Ixazomib is an oral, highly selective, and reversible proteasome inhibitor. It preferentially binds to and inhibits the chymotrypsin-like activity of the beta-5 subunit of the 20S proteasome. This results in the disruption of cellular regulatory mechanisms, which in turn inhibits cell growth and survival pathways, ultimately leading to apoptosis [86]. In the TOURMALINE-AL1 trial, ixazomib combined with dexamethasone did not show a higher rate of hematologic responses (53% vs. 51%) and did not meet the primary endpoint. However, several key secondary endpoints were met, including time to vital organ deterioration or death (35 vs. 26 months) and the hematologic complete response (CR) rate (26% vs. 18%). Hematologic responses were prolonged in the ixazomib/dexamethasone arm compared to the physician's choice arm (46.5 vs. 20.2 months). Additionally, the progression-free survival (PFS) of vital organs was also longer in the ixazomib/dexamethasone arm (18 vs. 11 months) [87]. Whether ixazomib is the preferred proteasome inhibitor in newly diagnosed AL amyloidosis with higher efficacy or a better safety profile needs further investigation. A phase 1/2 study of ixazomib with cyclophosphamide and dexamethasone in newly diagnosed AL amyloidosis (NCT03236792) demonstrated the safety and efficacy of the oral IxaCyD regimen. In the phase 1/2 intention-to-treat (ITT) population, an overall hematologic response rate of 55% was observed. With the recommended phase 2 dose (RP2D) (Ixa, 4 mg; Cy, 500 mg; D, 20 mg), 64% of patients achieved a hematologic response, including 57% who rapidly achieved a very good partial response (VGPR) after a mean of 1.5 cycles. This response resulted in renal responses in 50% of evaluable RP2D patients at 6 months, but only 22% showed cardiac responses at the same time point. This study demonstrated that IxaCyD is a safe and effective all-oral induction regimen for treatment-naïve patients with AL amyloidosis [88].

Immunomodulatory Drugs

Thalidomide

Thalidomide is associated with significant toxicities, particularly in AL amyloidosis with cardiac involvement (e.g., bradycardia and cardiac arrhythmia). Thalidomide should be avoided in patients with AL and pre-existing peripheral neuropathy (PNP) [76].

Lenalidomide

Lenalidomide is a second generation immunomodulatory drug (IMiD) used for treating patients with relapsed or refractory myeloma. Lenalidomide was combined with melphalan/dexamethasone or cyclophosphamide/dexamethasone at lower than standard doses, resulting in hematologic responses in 38-68% of previously untreated patients and 46-60% in patients refractory to bortezomib, thalidomide, and alkylating agents [89,90]. The median dose of lenalidomide was 10 mg per day (maximum 15 mg). Treatment discontinuations were frequent [91]. Lenalidomide-associated toxicities in AL amyloidosis patients include myelosuppression, skin rashes, infections, thrombotic complications, and fatigue.

Pomalidomide

Pomalidomide is an IMiD developed after thalidomide and lenalidomide. Before excretion, pomalidomide is mainly metabolized by CYP450 in the liver, and unlike lenalidomide, only 2% of unmetabolized pomalidomide is excreted in the urine [92]. Most patients exhibit an initial response after one cycle of therapy. Hematologic response was associated with improved overall survival (median survival: 50 vs. 27 months). At least partial hematologic responses were linked to significantly longer progression-free survival (PFS) (median PFS: 37 vs. 18 months). Grade 3 adverse events were documented in 33% of patients, with the most common adverse events being infections (9%), heart failure (7%), an increase in creatinine (6%), and cytopenia (2%) [93].

Iberdomide and Megzidomide are not yet approved for the treatment of MGRS.

Monoclonal Antibodies

Daratumumab

Daratumumab is a human monoclonal IgG1-κ antibody that binds to a single CD38 epitope [94]. In the phase 3 ANDROMEDA study, daratumumab subcutaneously combined with CyBorD (cyclophosphamide, bortezomib, dexamethasone) was compared with CyBorD in first-line therapy. The safety run-in phase demonstrated an excellent overall response rate of 96% in the Dara-CyBorD arm, with 82% achieving a very good partial response (VGPR). The study also showed that daratumumab plus CyBorD was well tolerated by previously untreated AL amyloidosis patients [73,95]. Based on these data, daratumumab was approved by the US FDA on January 15, 2021, for the treatment of AL amyloidosis. Notably, no new safety signals were observed, and daratumumab can be safely administered to patients with severe renal impairment (RI) or dialysis-dependent patients [97].

Isatuximab

Isatuximab is a chimeric mouse/human IgG1k monoclonal antibody targeting CD38 on both malignant and normal plasma cells. Its antitumor effect primarily results from antibody dependent cell mediated cytotoxicity. The efficacy of isatuximab in relapsed or refractory AL amyloidosis and MGRS is currently under investigation [96].

Elotuzumab

Elotuzumab is a humanized immunostimulatory IgG1 monoclonal antibody targeting the lymphocyte signaling activation molecule F7 (SLAMF7, also known as CS1), a glycoprotein expressed in myeloma and natural killer cells but not in normal tissue [98]. Elotuzumab combined with lenalidomide and dexamethasone showed a significant hematologic response in a patient with relapsed/refractory multiple myeloma (RRMM) and kFLC amyloidosis. This treatment combination alone may be effective in primary amyloidosis and warrants further investigation [99].

4.4. T-cell redirection therapies

Monoclonal Antibodies Targeting BCMA

Teclistamab

Teclistamab is a bispecific T-cell engager antibody that binds to B-cell maturation antigen (BCMA) on malignant plasma cells and CD3 on T cells, thereby redirecting cytotoxic T cells to eliminate BCMA-expressing clonal plasma cells. Although originally developed for relapsed/refractory multiple myeloma, recent evidence supports its use in systemic AL amyloidosis. In a retrospective multicenter study, Chakraborty et al. evaluated seven patients with relapsed AL amyloidosis treated with teclistamab, all of whom achieved a hematologic response of VGPR or better (100%), with rapid and deep suppression of free light chains and early organ response [69]. In a recent multinational retrospective case series evaluating teclistamab in relapsed or refractory AL amyloidosis, Forgeard et al. reported encouraging safety and efficacy signals in a heavily pretreated patient population. Importantly, no unexpected toxicity signals were observed, and cytokine release syndrome and neurotoxicity were manageable. These findings suggest that teclistamab may represent a promising therapeutic option for selected, heavily pretreated AL amyloidosis patients, particularly those who are ineligible for transplantation or refractory to conventional therapies [125].

Chimeric Antigen Receptor (CAR) T-Cells

T-cell therapy with chimeric antigen receptors (CARs) has emerged as a novel approach with the potential to provide long-term disease control in patients with some types of hematologic cancers. Anti-CD19 CAR-T cell therapies have been shown to be effective in patients with leukemia or lymphoma [104,105]. In a prospective study, clonal plasma cells from patients with AL amyloidosis were found to express low levels of BCMA but high levels of SLAMF7. SLAMF7 CAR-T cells showed antitumor activity in an AL amyloidosis model in a preclinical study. SLAMF7 CAR-T cells were injected into xenograft models of AL amyloidosis [106]. This suggests that CAR-T cells could have a role, particularly for a subset of AL amyloidosis patients. IgM AL amyloidosis, caused by an underlying lymphoproliferative/lymphoplasmacytic B-cell clone secreting intact IgM, occurs in 5-7% of cases [107]. Ongoing clinical trials are expanding the spectrum of disease to include indolent lymphomas.

Venetoclax

Venetoclax is a highly selective and potent oral BCL-2 inhibitor that induces apoptosis in multiple myeloma cell lines and primary multiple myeloma cells [108]. A retrospective study of 43 patients with relapsed/refractory AL showed that patients with t(11;14) had a higher overall hematologic response rate (81% vs. 40%) and a higher CR/VGPR rate (78% vs. 30%). The study also demonstrated a high rate of organ response (83% vs. 17%) and a reduced risk of progression or death (HR: 0.292, 95% CI: 0.046–1.855, p = 0.192) [109].

4.5. Therapy of MIDD

Small retrospective studies have suggested that HDM/ASCT is a good treatment option with high hematologic response rates and low treatment-related mortality [110]. Preliminary results suggest that bortezomib-based therapies may yield similar hematologic response rates to HDM/ASCT, as seen in multiple myeloma [111]. In patients with stage 1 to 3 chronic kidney disease (CKD), the primary goal is to preserve renal function. Bortezomib-based treatment, such as CyBorD, is recommended as initial treatment. HDM/ASCT should then be considered in selected patients who are in good general condition and lack significant extrarenal manifestations, particularly if they have only achieved a partial hematologic response to initial treatment. For patients with stage 4 and 5 CKD, the likelihood of renal recovery is low. In such patients who are not candidates for kidney transplantation, the primary goal is to preserve extrarenal organs, especially the heart. Bortezomib-based therapy, such as CyBorD, is recommended. If renal transplantation is planned, the therapeutic goal is long-term preservation of allograft function, requiring an optimal clonal response. In this case, HDM/ASCT should be considered after 3 to 4 cycles of CBD-like therapy [112].

Type I Cryoglobulinemia

Type I cryoglobulinemia is typically associated with a monoclonal IgG, IgA, or IgM produced by an underlying plasma cell or B-cell clone. Management is dictated by the severity of systemic manifestations and the nature of the clonal disorder. Patients with mild symptoms and low-grade clonal proliferation may be monitored with serial renal assessments. Cold avoidance and symptomatic treatment remain essential. Treatment is indicated in patients with progressive vasculopathy, hyperviscosity, or renal involvement.

Plasma cell driven type I cryoglobulinemia (usually IgG/IgA):

Therapy should follow myeloma type regimens. Bortezomib-, cyclophosphamide-, and thalidomide based therapies are effective in rapidly reducing cryoglobulin production and stabilizing renal function.

Rituximab is not effective in this subtype because the pathogenic clone is not CD20-positive [132].

Lymphoplasmacytic / IgM-associated type I cryoglobulinemia:

Treatment should align with WM or IgM driven MGRS, typically rituximab containing therapy, combined with steroid premedication to minimize IgM flare. Bendamustine-rituximab is appropriate in progressive disease and remains safe in renal impairment [133].

Type I cryoglobulinemia due to underlying CLL or B-cell lymphoma:

Treatment should follow CLL/lymphoma protocols using anti-CD20 antibodies combined with cytotoxic agents as indicated [54].

Cyclophosphamide dose reduction is required when GFR <20 mL/min, while bendamustine is advantageous because it is not renally eliminated [113].

Plasma exchange may be considered for patients with severe hyperviscosity or rapidly progressive vasculitis while clone directed therapy is initiated.

Type II Cryoglobulinemia

Most cases are associated with chronic hepatitis C virus (HCV) infection [114]. Antiviral therapy should be administered to all patients with symptomatic type II cryoglobulinemia linked to chronic HCV infection. In patients with symptomatic vasculitis, antiviral therapy should be combined with rituximab. Complete plasma exchange should also be considered in patients with rapidly progressive renal disease and/or severe organ involvement [115]. For patients without detectable viral replication but who experience episodic purpuric relapses, monitoring alone is recommended. For recurrent symptoms or renal involvement, rituximab is the treatment of choice [116]. Chemotherapy should be considered in patients with manifest Waldenström's disease or B-cell lymphoma, particularly if symptoms are more severe than occasional purpura, regardless of their HCV status. The treatment regimen should be adjusted based on the underlying B-cell clone and renal function [117].

Immunotactoid Glomerulopathy

Glomerulonephritis with organized microtubular monoclonal immunoglobulin deposits is often associated with CLL or small lymphocytic lymphoma in more than half of cases, while a low-grade plasma cell clone is less common. Although therapy selection is based on limited case series, treatment adapted to CLL should be proposed for most patients. In severe CKD, cyclophosphamide- and/or bendamustine-based therapies, including corticosteroids, may be recommended. In patients with manifest CLL, rituximab should be considered. In cases of gammopathy, the role of rituximab is uncertain, and bortezomib-based therapy may be an option [118].

PGNMID

Proliferative glomerulonephritis with monoclonal immunoglobulin deposits (PGNMID) represents a heterogeneous MGRS entity in which therapeutic decisions depend on the nature of the underlying clone. In patients with stage 1-2 CKD and non-progressive low grade proteinuria (<1 g/day), conservative management with close monitoring may be appropriate, as spontaneous partial remissions have been reported [126]. However, patients with persistent proteinuria >1 g/day, declining renal function, or stage 3-4 CKD generally require clone-directed therapy. For plasma cell driven PGNMID, cyclophosphamide–bortezomib–dexamethasone (CBD-like therapy) is widely utilized due to its rapid cytoreductive effect, favorable renal tolerability, and high rates of hematologic response [127]. The term “CBD-like” refers to combinations structurally equivalent to CyBorD but adjusted for renal insufficiency. Bortezomib, as a proteasome inhibitor with rapid activity and no need for renal dose adjustment, remains the cornerstone of therapy for plasma cell mediated MGRS lesions, including PGNMID and LCDD [128]. Subcutaneous once-weekly bortezomib is preferred in CKD to minimize neuropathy while preserving efficacy.

In patients with significant cytopenias, severe CKD, or frailty, CyBorD (cyclophosphamide, bortezomib, dexamethasone) is considered an optimal first-line option because of its predictable safety profile and effectiveness even in dialysis dependent patients [129]. Autologous stem cell transplantation (HDM/ASCT) may be considered in selected fit patients with plasma cell associated PGNMID, particularly when partial hematologic response persists after initial therapy [130].

B-cell / lymphoplasmacytic PGNMID

For patients with B-cell or lymphoplasmacytic clones (e.g., IgM PGNMID), rituximab based regimens constitute the foundation of therapy. Combination therapy (e.g., rituximab–bendamustine) may be necessary in proliferative or relapsing disease. Bendamustine is particularly valuable in advanced CKD because it is not renally excreted and requires no dose adjustment [131].

Acquired Fanconi Syndrome

In rare cases of symptomatic progression, steroids should be considered in addition to chemotherapy. For patients with stage 1 to 3 CKD, chemotherapy may help slow the progression of end-stage renal disease (ESRD). Cyclophosphamide-, bortezomib-, or thalidomide-based therapies are the best options, with bendamustine also being a viable alternative. HDM/ASCT may be considered for selected non-responding patients, though its benefit remains unproven. For patients with stage 4 to 5 CKD who are candidates for renal allograft transplantation, chemotherapy (including HDM/ASCT) should be considered before and/or after transplantation. For those not eligible for kidney transplantation, chemotherapy is not beneficial [54].

5. Conclusions

Monoclonal gammopathy of renal significance (MGRS) encompasses a heterogeneous group of kidney diseases caused by nephrotoxic monoclonal immunoglobulins produced by small B-cell or plasma cell clones that do not meet criteria for overt hematologic malignancy. Early recognition is essential, as renal injury can progress rapidly and become irreversible. A renal biopsy remains the cornerstone of diagnosis, allowing precise identification of the underlying lesion and its pathophysiological mechanism. Effective management requires close collaboration between nephrology and hematology to ensure timely, clone-directed therapy aimed at halting further organ damage and stabilizing or improving kidney function. Advances in diagnostic techniques and targeted treatments including novel immunotherapies are expanding therapeutic options and improving outcomes. Despite these developments, MGRS remains a progressive disorder if untreated, underscoring the importance of early diagnosis, individualized therapy, and ongoing multidisciplinary care.

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