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CRITICAL REVIEW

# The evaluation and management of monoclonal gammopathy of renal significance and monoclonal gammopathy of neurological significance

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## Abstract

Despite the benign nature of monoclonal gammopathy of undetermined significance (MGUS), mounting data are associating MGUS with the development of organ dysfunction, specifically monoclonal gammopathy of renal significance (MGRS) and monoclonal gammopathy of neurological significance (MGNS), which could be associated with substantial morbidity. Emerging evidence suggests that patients with MGRS and MGNS could benefit from treatments used for myeloma, Waldenström macroglobulinemia, or chronic lymphocytic leukemia, depending on the underlying pathology. However, the treatment of MGRS and MGNS is not standardized, and potentially effective therapies might not be reimbursed because these conditions do not formally meet the criteria for malignant processes. The present review aims at establishing standards for the evaluation and management of MGRS and MGNS, which can facilitate the diagnosis of and provide therapeutic options for treating practitioners and patients affected by these conditions. The careful design and execution of clinical trials for patients with MGRS and MGNS are positively encouraged.

## 1 | INTRODUCTION

Monoclonal gammopathy of undetermined significance (MGUS) is a benign condition with malignant potential. Based on the associated paraprotein, MGUS can be separated into two distinct groups, non-IgM MGUS, including IgG, IgA, and kappa or lambda free light chain (FLC) MGUS, and IgM MGUS. Upon progression, most individuals with non-IgM MGUS tend to develop multiple myeloma (MM) or systemic light chain (AL) amyloidosis,[1] while most individuals with IgM MGUS progress into WM or other lymphoproliferative disorders.[2]

Despite its benign nature, MGUS can associate with organ dysfunction. Monoclonal gammopathy of renal significance (MGRS) and neurological significance (MGNS) can induce different degrees of morbidity and potential disability. Clinical experience suggests that patients with MGRS and MGNS could benefit from treatments used for hematologic malignancies. The treatment of MGRS and MGNS, however, is not standardized, and effective therapies might not be offered or reimbursed because these conditions do not meet the criteria for malignancy.

This review provides guidance on the evaluation, diagnosis, and management of patients with MGRS and MGNS.

## 2 | MONOCLONAL GAMMOPATHY OF RENAL SIGNIFICANCE

### 2.1 | Definition of MGRS

In 2012, the International Kidney and Monoclonal Gammopathy Research Group (IKMG) formally defined MGRS as hematological

clonal disorders that produce a monoclonal paraprotein associated with renal damage.[3] In 2017, the IKMG updated the definition of MGRS to include any hematological condition, not only a malignancy, associated with a nephrotoxic monoclonal paraprotein causing renal injury.[4] Therefore, the current diagnosis of MGRS does not require the presence of defined lymphoma or myeloma.

## 2.2 | MGRS-associated renal lesions

The diagnosis of MGRS can only be established with renal biopsy. The classification of MGRS-associated renal lesions proposed by the IKMG in 2017 is based on light microscopy, immunofluorescence studies, and electron microscopy (EM) findings on material obtained from such biopsies.[4] Light microscopy and immunofluorescence are mandatory for proper evaluation of MGRS. Note, EM evaluation is encouraged but not required, given accessibility limitations. The findings of light chain cast nephropathy, or monoclonal plasma cell infiltration in the kidney biopsy, represent multiple myeloma diagnoses and must be managed accordingly. The classification of MGRS-associated renal lesions is shown in Table 1.

## 2.3 | Evaluation of MGRS

A kidney biopsy is at the center of the evaluation of MGRS. However, it is essential to evaluate patients for other causes of kidney dysfunction. A study showed that about half of the patients with concurrent MGUS and chronic kidney dysfunction did not have MGRS lesions on kidney biopsy.[5] The risk of under diagnosis should be balanced against the risk of the procedure itself, especially in frail patients in whom treatment might not be pursued. Renal biopsies have been associated with a small risk of bleeding.[6] A transjugular kidney biopsy is an option in patients at high risk for complications from transcutaneous biopsy.[7] A suggested algorithm for the evaluation of renal biopsy in MGRS patients is shown in Figure 1.

The diagnosis of MGRS is established by integrating the findings from a kidney biopsy, as well as the patient's medical history, bone marrow biopsy, imaging, and laboratory data. We recommend the kidney biopsy material be reviewed by a pathologist with experience in this area. For confirmation of monoclonal immunoglobulin deposits, immunofluorescence staining for IgG subclasses, IgA and IgM, as well as light chains, is recommended. Heavy chain restriction is not sufficient to establish monoclonality as some non-MGRS lesions can show IgG subclass restriction.[8] Positive staining for C1q or C3 proteins can be seen in patients with MGRS lesions such as PGNMID, immunotactoid glomerulonephritis, type I cryoglobulinemic glomerulonephritis, C3 glomerulonephritis, and monoclonal immunoglobulin deposition disease (MIDD). Pronase digestion might be used for unmasking immunoglobulins in paraffin-fixed samples.[9] Electron microscopy should be performed on glutaraldehyde-fixed tissue. Paraffin-embedded tissue can be repurposed for EM. Electron microscopy evaluation should include at least two glomeruli, as glomerular deposits can be scattered and

**TABLE 1** Classification of monoclonal gammopathy of renal significance-associated renal lesions

| Monoclonal immunoglobulin deposits | | | | |
|---|---|---|---|---|
| **Organized** | | | | |
| **Fibrillar** | **Microtubular** | **Inclusions or crystalline deposits** | **Non-organized** | **No monoclonal immunoglobulin deposits** |
| AL amyloidosis<br>• Congo red positive<br>• Fibril diameter: 7–12 nm<br>Monoclonal fibrillary glomerulonephritis<br>• Congo red negative<br>• Fibril diameter: 10–30 nm | Immunotactoid glomerulonephritis<br>• Diameter: 17–52 nm, hollow<br>• Parallel distribution<br>Cryoglobulinemic glomerulonephritis<br>• Diameter: 17–52 nm, hollow<br>• Not organized | Light chain proximal tubulopathy<br>• Crystalline variant: *kappa*, Fanconi syndrome common<br>• Non-crystalline variant: *lambda*, Fanconi syndrome rare<br>Crystal storing histiocytosis<br>• Renal histiocytes<br>• BM, LN, lungs<br>Crystal globulin glomerulonephritis<br>• Ig thrombi in glomerular capillaries | Monoclonal immunoglobulin deposition disease<br>• Light or heavy chains distributed along GBM and TBM<br>• IgG1<br>Proliferative glomerulonephritis and monoclonal immunoglobulin deposition<br>• Glomerular deposition<br>• IgG3, IgA, IgM (rare) | C3 glomerulopathy with monoclonal gammopathy<br>• Monoclonal gammopathy detectable in 60–80% of individuals >50 years with C3 glomerulonephritis<br>Thrombotic microangiopathy<br>• Provisional<br>POEMS<br>• Provisional |

*Note:* Adapted from[4].

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

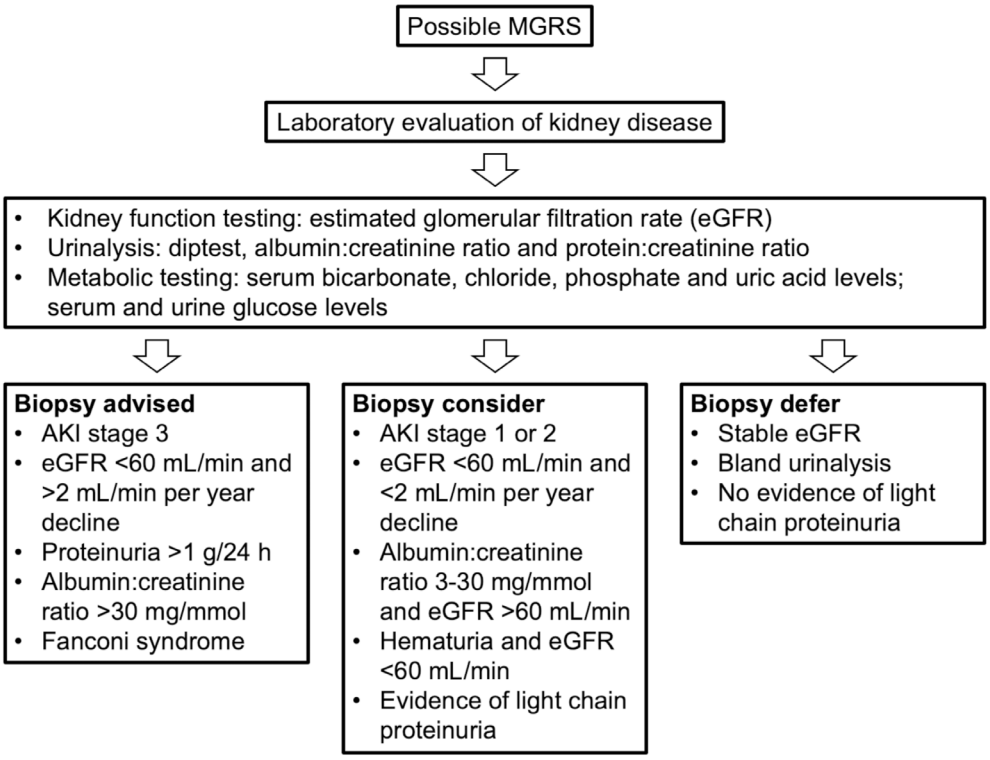


**FIGURE 1** Proposed algorithm for renal biopsy in patients with monoclonal gammopathy of renal significance. Adapted from.[4] AKI, acute kidney injury; MGRS, monoclonal gammopathy of renal significance

infrequent, and the tubule basement membrane should be examined for crystals or inclusions. Immunohistochemistry and laser microdissection followed by liquid chromatography and mass spectrometry are recommended for the evaluation of AL amyloidosis.

Once MGRS has been diagnosed, all efforts should be made to identify the presence of a monoclonal process and make the correct disease categorization. Serum and urine protein electrophoresis with immunofixation, serum FLC levels, and 24-hour urine protein quantification should be obtained. The monoclonal paraprotein detected in serum or urine must match the one in the renal biopsy. Additional testing should include bone marrow aspirate and biopsy, advanced imaging studies, excisional lymph node biopsy, and/or peripheral blood flow cytometry, as clinically indicated. If the evaluation above is diagnostic of MM, WM, AL amyloidosis, CLL, or other lymphoproliferative disorders, the patient should be managed following the respective algorithm.

## 2.4 | Treatment of MGRS

Treatment recommendations were provided by the IKMG in 2012.[10] Without active therapy against the B-cell clone producing the nephrotoxic monoclonal paraprotein, the natural course of MGRS is characterized by progressive renal dysfunction followed by end-stage renal disease (ESRD). The choice of therapy should take into account the patient's age, clinical presentation, comorbidities, genomic profiling, and preferences, and the drug's renal metabolism and potential renal toxicity. Working with a nephrologist with experience is positively encouraged.

Non-IgM and FLC-associated MGRS should be managed as per the treatment algorithm for MM unless another lymphoproliferative disorder is confirmed. According to the International Myeloma Working Group recommendations for the management of MM-related renal impairment, the use of most of the standard treatment options available for the treatment of MM is safe and effective in patients with renal dysfunction.[11] Immunomodulating agents (e.g., thalidomide and pomalidomide) and proteasome inhibitors (e.g., bortezomib, carfilzomib, and ixazomib) can be used in MM patients with renal impairment without dose adjustments, while other drugs such as lenalidomide require dose modifications. The safety and efficacy of daratumumab and elotuzumab have been demonstrated in MM patients with renal dysfunction.[12-16] High-dose chemotherapy followed by autologous stem cell transplantation (ASCT) can be a treatment option in patients with MM renal impairment, including those with ESRD.[11] In rare cases in which MGRS is accompanied by a solitary plasmacytoma, local radiation therapy can achieve control of the renal damaging paraprotein.[17]

IgM-associated MGRS should follow the treatment algorithm for WM. Cyclophosphamide and bendamustine are preferred over melphalan or fludarabine, given melphalan toxicity in patients with reduced renal function and fludarabine-associated renal metabolism as well as the stem cell toxicity associated with these agents.[18,19] Bendamustine can be safely used at reduced doses in patients with abnormal renal function. Proteasome inhibitors and rituximab can be safely used in the setting of renal dysfunction without dose adjustments.[20] The Bruton tyrosine kinase (BTK) inhibitor ibrutinib can be used in patients with an estimated glomerular filtration rate (GFR) >25 mL/min.[21-23]

In MGRS cases with underlying features consistent with monoclonal B-lymphocytosis, treatments for chronic lymphocytic leukemia (CLL) should be considered. Bendamustine, cyclophosphamide, rituximab, and ibrutinib can be safely administered in patients with renal dysfunction. Similar to rituximab, ofatumumab and obinutuzumab can be safely administered in patients with renal impairment. Venetoclax does not need dose adjustments in patients with estimated GFR >30 mL/min.[24-26]

The hematological response should be assessed using the response criteria for MM in non-IgM and criteria for WM in IgM-associated MGRS. In MGRS cases in which the causal monoclonal paraprotein is challenging to measure, the response should be assessed using renal function, resolution or improvement in proteinuria, bone marrow involvement, or radiological findings. More sensitive approaches for the detection of monoclonal protein, such as mass spectrometry, may be useful in patients where traditional immunofixation approaches do not detect a monoclonal protein. The goal of therapy should focus on preventing further renal damage by the monoclonal paraprotein and allowing for recovery of such damage. Therefore, pursuing a deep response characterized by hematological response and disappearance of the serum monoclonal gammopathy and normalization of FLC ratio is reasonable. Renal response to therapy should be assessed following the criteria established by the International Myeloma Working Group in 2010.[27] Evidence of relapse of the nephrotoxic monoclonal paraprotein should prompt reinitiation of therapy based on treatment algorithms for MM, WM, AL amyloidosis, or CLL. Treatment at relapse should be tailored, considering the response to and toxicity of prior therapy, patient's performance status, and renal function at the time of relapse.

## 3 | MONOCLONAL GAMMOPATHY OF NEUROLOGICAL SIGNIFICANCE

### 3.1 | The definition of MGNS

The association between MGUS and peripheral neuropathy (PN) was established in a population-based study in which the relative risk of PN was increased in individuals with MGUS.[28] However, the relation between the monoclonal gammopathy and PN may not be causal. Therefore, the evaluation of MGNS is crucial to increase or decrease our concerns of an association between monoclonal gammopathy and concurrent PN.

Monoclonal IgM paraprotein is more commonly associated with PN than IgG or IgA paraproteins.[29] Clinical and electrophysiological features are more heterogeneous in IgG/IgA than in IgM MGNS and can be indistinguishable from chronic idiopathic demyelinating polyneuropathy (CIDP).[30] No specific antibody has been associated with IgG/IgA demyelinating PN, and there is no need to test for anti-myelin-associated glycoprotein (MAG) or anti-ganglioside antibodies. Axonal PN is often present in patients with IgA/IgG MGUS, but a pathogenic relation is currently unclear, except for patients with AL amyloidosis and POEMS syndrome.[31] The diagnostic workup for a patient with PN and IgG/IgA MGUS should include evaluation for other PN causes (e.g., diabetes, cobalamin deficiency, and chronic alcohol use), AL amyloidosis, and POEMS syndrome, as well as nerve conduction studies (NCS). The management of PN in patients with IgG/IgA MGUS should mimic the management of CIDP without paraproteinemia.[30] From here forward, MGNS refers to IgM-mediated PN.

Unlike MGRS, in which a kidney biopsy is relatively safe, a nerve biopsy in MGNS can be associated with permanent sensory or motor deficits and pain in the area distal to the biopsy and is less desirable as a diagnostic method. Without the routine use of definitive methods of establishing a relation between the monoclonal paraprotein and PN, the diagnosis of MGNS would be one of exclusion. We strongly encourage a coordinated effort with neurologists for the diagnosis and management of MGNS.

### 3.2 | MGNS-associated neurological syndromes

IgM-mediated PN is typically associated with sensory (rather than motor) deficits of symmetrical distribution, length-dependent (ie, it affects toes and feet before it affects fingers and hands), and of slow progression (i.e., over months to years rather than weeks to months) in the context of an IgM paraproteinemia. This clinical syndrome is known as distal acquired demyelinating symmetric neuropathy with monoclonal gammopathy (DADS-M).[32] The progression of DADS-M is insidious and, in up to 50% of patients, significant disability develops 10–15 years after the diagnosis.[33]

High titers of anti-MAG antibodies can be detected in approximately half of the patients with DADS-M. The presence of anti-MAG antibody titers, however, has no impact on the severity of the PN. In patients with positive anti-MAG antibody titers, strongly positive titers (>70 000 Bühlmann units) are considered clinically significant, while lower titers are less specific for DADS-M with anti-MAG antibodies.[34] Low anti-MAG titers (<200 Bühlmann units) can be detected in 15% of individuals without IgM monoclonal paraprotein.[35] In patients with DADS-M and negative anti-MAG antibodies, antibodies against gangliosides as well as sulphate-3-glucuronyl paragloboside (SGPG) should be evaluated.

Chronic ataxic neuropathy with ophthalmoplegia, monoclonal gammopathy, cold agglutinins, and disialosyl ganglioside (anti-GD1b, anti-GT1b or anti-GQ1b) antibodies (CANOMAD) is a rare condition characterized by PN, ataxia, ophthalmoplegia, and sometimes other cranial nerve involvement.[36] NCS show mixed axonal and demyelinating features.

The spectrum of MGNS is likely to keep expanding. More research needs to be done to understand and define better the multiple clinical syndromes associated with MGNS.

### 3.3 | Evaluation of MGNS

Recommendations from a consensus panel on the investigation of IgM and WM-associated PN have been published.[34] A list of tests used to classify, diagnose and evaluate MGNS is shown in Table 2.

**TABLE 2** Tests to consider for evaluation of monoclonal gammopathy of neurological significance

| Laboratory tests | Radiological tests | Pathological tests | Neurological tests |
|---|---|---|---|
| Complete blood count | CT scan of the chest, abdomen and pelvis with IV contrast | Bone marrow biopsy | Nerve conduction studies |
| Comprehensive metabolic panel | PET/CT scan | MYD88 mutation analysis | Electromyography |
| SPEP with immunofixation | Skeletal survey | CSF cytology and flow cytometry | |
| Serum immunoglobulin levels | Whole-body MRI | Fat pad biopsy | |
| Serum free light chain levels | Brain and spine MRI with gadolinium | Nerve biopsy | |
| Cryoglobulins | | | |
| Anti-MAG antibodies | | | |
| Anti-ganglioside antibodies | | | |
| Hemoglobin A1c, fasting glucose or OGTT | | | |
| Serum cobalamin level | | | |
| Serum TSH level | | | |
| HIV antibody testing | | | |
| Lyme antibody testing | | | |
| Syphilis testing | | | |
| ANA titer | | | |
| Serum troponin levels | | | |
| Serum NT-proBNP levels | | | |
| VEGF level | | | |

Abbreviations: ANA, antinuclear antibody; BNP, brain natriuretic peptide; CSF, cerebrospinal fluid; CT, computerized tomography; MAG, myelin-associated glycoprotein; MRI, magnetic resonance imaging; OGTT, oral glucose tolerance test; PET, positron emission tomography; SPEP, serum protein electrophoresis; TSH, thyroid stimulating hormone; VEGF, vascular endothelial growth factor.

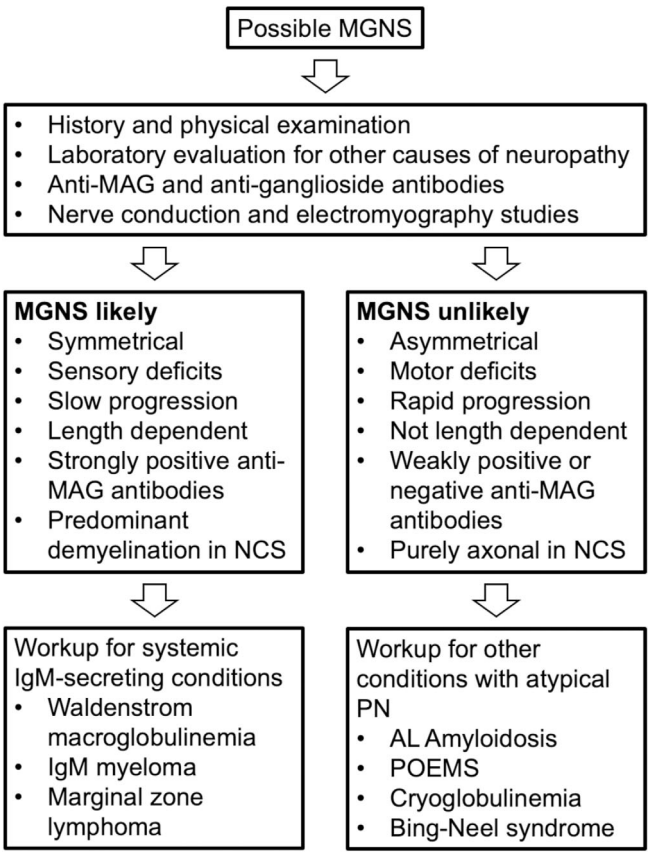


**FIGURE 2** Proposed algorithm for evaluation of patients with monoclonal gammopathy of neurological significance. Adapted from.[34] MAG, myelin-associated glycoprotein; MGNS, monoclonal gammopathy of neurological significance; NCS, nerve conduction studies; PN, peripheral neuropathy; POEMS, polyneuropathy, organomegaly, endocrinopathy, monoclonal gammopathy, and skin changes

The first step in the evaluation of MGNS is to investigate other more common causes of neuropathy, such as chronic alcohol intake, diabetes, cobalamin deficiency, HIV infection, and autoimmune conditions. Also, other conditions associated with an IgM paraprotein, such as WM, cryoglobulinemia, AL amyloidosis, and Bing-Neel syndrome (BNS), should be evaluated. Note, BNS is a rare condition in which WM cells gain access to the central nervous system causing neurological deficits.[37] The BNS patients can present with atypical sensorimotor PN and symptoms related to brain or spinal involvement, such as seizures, cranial nerve symptoms, headaches, and limb pain. A suggested algorithm for the evaluation of MGNS patients is shown in Figure 2.

The next step in the evaluation of MGNS is to obtain NCS. In IgM-mediated neuropathy, NCS reveals a demyelination pattern characterized by slow motor conduction velocities, prolonged distal latencies, and low terminal latency indices with reduced or absent sensory responses.[38] Demyelination is the hallmark of MGNS, while purely axonal features should prompt evaluation for other neuropathy causes. Prolonged, chronic demyelination can induce secondary axonal damage. In cases where the NCS is normal, small fiber neuropathy (SFN) should be suspected and potential causes evaluated. SFN is not considered an MGNS-related syndrome at the moment.[34]

A causal relation is less likely in MGNS if the PN is purely axonal, if the time to the peak of PN symptoms is shorter than 6 months, if PN has a relapsing and remitting course, if there is cranial nerve involvement (with the specific exceptions of CANOMAD or BNS), if there is a non-symmetrical distribution or if there is a history of a viral infection 2 to 4 weeks before the onset of symptoms. Other conditions should be evaluated in cases with these features, including AL amyloidosis, POEMS syndrome, and cryoglobulinemia. AL amyloidosis can present with pain and mixed sensory and motor deficits with or

without signs of autonomic nervous system damage, such as bowel and bladder dysfunction or orthostatic hypotension.[39] A classic presentation is bilateral carpal tunnel syndrome. The POEMS syndrome-associated neuropathy develops within weeks or months and presents with prominent pain and motor deficits such as weakness in proximal muscles.[40] Cryoglobulinemia can associate with vasculitic neuropathy, which progresses over weeks and is characterized by asymmetrical pain, weakness, and sensory deficits.[41] A classic presentation of vasculitic neuropathy is mononeuritis multiplex.

Once MGNS is diagnosed, all efforts should be made to rule out a systemic malignant process, such as WM, MM, or other lymphoproliferative disorders associated with IgM secretion.

### 3.4 | Treatment of MGNS

Data on the treatment of MGNS is limited to a few underpowered randomized studies, retrospective studies, and case reports. Based on scant data, patients with DADS-M without anti-MAG antibodies seem to have lower response rates to immunomodulating therapies with intravenous immunoglobulin (IVIG), steroids, or plasma exchange than idiopathic CIDP.[42] So, IVIG therapy has not been associated with long-term benefit in DADS-M without anti-MAG antibodies.[43,44] In DADS-M with anti-MAG antibodies, IVIG and steroids have shown to be of little help.[45,46] Alkylating agents and nucleoside analogs have shown modest efficacy in small studies.[47] The efficacy of rituximab monotherapy has been associated with clinical benefit in some studies,[48-50] but other studies show worsening of PN on rituximab.[51,52] However, the worsening in PN might have been associated with an IgM flare. Two small, and likely underpowered, randomized studies evaluating rituximab against placebo in anti-MAG positive PN did not meet their endpoints of clinical benefit.[53,54] However, there were improvements in secondary outcomes, and a systematic review supported therapeutic benefit.[46] A retrospective study has suggested that combination chemoimmunotherapy might be more effective than monotherapy in IgM-mediated PN.[48] In patients with CANOMAD, IVIG and rituximab have shown clinical benefit.[55] There is a scarcity of data on the treatment of MGNS mediated by cryoglobulins or anti-ganglioside antibodies.

Overall, the treatment of MGNS represents a challenge. The panel recommends treating patients with a high suspicion for an IgM-related MGNS (i.e., bilateral and symmetrical sensory deficits, length dependency, slow progression, high anti-MAG antibody titers, and demyelination in NCS) with PN symptoms affecting the patient's activities of daily living. Observation is reasonable for patients with low suspicion of IgM-related MGNS or in patients with mild symptoms. Treatment should follow the guidelines for WM. Neurotoxic agents, such as bortezomib or vincristine, should be avoided. Alkylating agents (e.g., cyclophosphamide and bendamustine), proteasome inhibitors with lower rates of PN (e.g., carfilzomib and ixazomib), and BTK inhibitors (e.g., ibrutinib), alone or in combination with anti-CD20 monoclonal antibodies (e.g., rituximab and ofatumumab) have been used in WM patients with IgM-associated PN.[21,23,56-58]

Response to therapy should follow the response criteria for patients with WM.[59] The treatment goal would be to attain deep responses to provide the best chance of inducing clinical benefit. However, the neurological improvement might be delayed for several months to a few years, even after serum IgM responses are obtained. In many cases, the neurological deficit is irreversible. There is no standardized approach to measuring neurological response in MGNS, and for now, response assessment relies on patient-reported outcomes. Prospective studies focusing on MGNS would have to include specific and reproducible eligibility criteria and validated PN monitoring methods.

## 4 | CONCLUSION

Both MGRS and MGNS are conditions associated with increased morbidity in the patients who suffered from them. As of today, these have been "benign" conditions, which true incidence is unknown due to lack of diagnostic standardization. Also, current therapeutic options are limited, non-standardized, and unlikely to induce clinical benefits. The panel proposes that patients with MGRS and MGNS should be managed following the recommendations for evaluation and treatment for MM and WM, not only to provide practitioners with a wider variety of treatment options but also to provide patients with opportunities to improve their quality of life. The panel encourages the careful design and execution of multicentric, prospective clinical trials exclusively focused on improving outcomes in patients with MGRS and MGNS to move from experience-based to evidence-based recommendations.

### CONFLICT OF INTEREST

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### DATA AVAILABILITY STATEMENT

No dataset is associated with this manuscript.

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