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REVIEW

Monoclonal Gammopathy-Associated Neuropathy

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Abstract

Purpose of Review Peripheral neuropathy (PN) is more commonly seen in individuals with monoclonal gammopathies, especially in patients with an IgM monoclonal gammopathy or Waldenström macroglobulinemia.

Recent Findings There are multiple potential ways that the paraprotein may result in peripheral neuropathy. The diagnosis and management of monoclonal gammopathy-associated PN are challenging and necessitate a concerted effort between the hematologist/oncologist and the neurologist.

Summary This review describes the most common PN syndromes associated with monoclonal gammopathy, such as anti-myelin-associated glycoprotein neuropathy, light chain amyloidosis, cryoglobulinemia, POEMS, CANOMAD, and others. We also review the therapies used to treat these conditions.

Keywords Monoclonal gammopathy · Neuropathy · Waldenström macroglobulinemia · Amyloidosis · CANOMAD · Anti-MAG · POEMS · Cryoglobulinemia

Introduction

Monoclonal gammopathy of undetermined significance (MGUS) is a benign condition that affects 3.2% of patients over 50 and 5.3% of those over 70 [1]. The most common isotype of MGUS is IgG (56%), followed by IgM (20%), IgA (12%), and less commonly light chain (5.5%), biclonal (6%), and IgD (0.5%) [2]. MGUS is a premalignant condition that has a risk of about 1% per year of progressing to a malignancy such as Waldenström macroglobulinemia (WM) or multiple myeloma [3]. MGUS is typically not associated with symptoms. Still, in some cases, the monoclonal paraprotein can cause organ dysfunction or other clinical manifestations such as renal disease, peripheral neuropathy (PN), or dermatologic conditions [4]. The paraproteinemia in these cases is referred to as a monoclonal gammopathy of clinical significance.

PN is one of the most common clinical manifestations related to a monoclonal paraprotein. PN affects 1–7% of the general population but occurs more frequently in patients with MGUS [5, 6]. A Swedish case–control study of participants with PN, including 15,351 with MGUS and 58,619 controls, demonstrated a prevalence of 7% and 3%, respectively, with a 2.7-fold risk of peripheral neuropathy in patients with MGUS compared with matched controls. Additionally, those with MGUS and diabetes had a 2.1-fold increased risk of PN compared with those with diabetes alone. PN occurs most frequently in patients with IgM monoclonal gammopathy compared with IgG or IgA gammopathy, with a prevalence of up to 31% in those with an IgM paraprotein [7–9]. PN is less common in IgA and IgG monoclonal gammopathy at approximately 14% and 6%, respectively.

In patients with MGUS and coexistent PN, it is essential to understand the etiology of the neuropathy and establish whether there is a connection between the peripheral neuropathy and the monoclonal gammopathy before initiating paraprotein-directed therapy. The two may be coincident without a pathogenic connection. There are multiple potential ways that the paraprotein may result in peripheral neuropathy, however, including light chain (AL) amyloidosis,

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autoantibodies against anti-myelin-associated glycoprotein (MAG), or cryoglobulinemia. Other unique syndromes include polyneuropathy, organomegaly, endocrinopathy, monoclonal protein, and skin changes (POEMS), and chronic ataxic neuropathy, opthalmoplegia, immunoglobulin M paraprotein, cold agglutinins, and disialosyl antibodies (CANOMAD) syndrome. Specific, recognizable clinical phenotypes of neuropathy are expected with each condition. The involvement of other organ systems may provide diagnostic clues, such as in AL amyloidosis. Finally, particular laboratory or electrodiagnostic testing findings may help establish one of these specific diagnoses and, therefore, the link between the paraprotein and the PN.

A review of the most common paraprotein-associated neuropathies, as well as an algorithm for evaluating patients with concomitant peripheral neuropathy and monoclonal gammopathy, can be found below.

Anti-MAG Neuropathy

Anti-MAG antibodies are the most common IgM-associated autoantibody and are typically detected in patients with IgM MGUS, WM, or other low-grade B-cell lymphomas. Approximately 40–50% of patients with concurrent IgM paraprotein and PN have an anti-MAG antibody [10]. Identifying low titers of anti-MAG antibodies may be non-specific, but high titers (> 70,000 Buhlmann units) are generally considered clinically relevant [11]. Anti-MAG antibodies can be detected in patients with other clinical conditions, such as IgM-related AL amyloidosis, so additional workup should be pursued even in the presence of an anti-MAG antibody if the clinical picture is not characteristic for anti-MAG neuropathy or if other diagnoses are suspected. The clinical picture of amyloid neuropathy is distinct from typical anti-MAG neuropathy, as described below [12, 13].

The neuropathy associated with anti-MAG antibodies is thought to be related to a direct effect of the IgM paraprotein on the nerves, resulting in nerve demyelination and a slowly progressive, symmetric, length-dependent demyelinating sensory neuropathy [14, 15]. Patients affected by anti-MAG neuropathy typically experience numbness in the feet first, with or without neuropathic pain. As the neuropathy progresses, distal weakness occurs, and with continued progression the hands can also be affected. Sensory ataxia is common and can result in gait impairment. Cranial nerve involvement, severe autonomic dysfunction, and proximal muscle weakness are rare. Nerve conduction studies and electromyography (NCS/EMG) characteristically show a demyelinating neuropathy with disproportionate prolongation of distal motor latencies. Features of secondary axonal degeneration can be present, especially with a longer duration of disease [16].

When anti-MAG neuropathy is identified in a patient with an underlying diagnosis of WM, WM-directed therapy may be indicated [17]. The timing of treatment initiation, however, can be nuanced as outlined in "Treatment approach in clinical practice" below. A standard therapy for the treatment of anti-MAG neuropathy in patients with MGUS has yet to be established. There are mixed reports of success using single-agent rituximab [18–22]. One randomized, double-blind, placebo-controlled trial included 54 patients randomized to rituximab 375 mg/m2 IV for four weekly doses or placebo. The primary outcome was the mean change in the inflammatory neuropathy cause and treatment (INCAT) sensory sumscore (ISS). No difference was noted in the ISS at 12 months, but improvements were seen in the INCAT disability scale, the self-evaluation scale, and two sub-scores on the Short Form-36 questionnaire [22]. Six-year follow-up of a subset of these patients showed no difference in ISS or the secondary outcomes, except for a worse 10-min walk test in patients who received a placebo. However, most of the patients in the placebo group had received other types of immunotherapy after the initial trial enrollment [21]. A retrospective case series of 7 patients treated with rituximab showed four patients with improvement in paresthesias, allodynia, tremor, and gait with neurologic exam demonstrating improvement in distal strength, vibration, and proprioception with resolution of Romberg sign and re-emergence of lower extremity reflexes [23]. Those who responded to treatment had shorter duration of symptoms, lower anti-MAG titers, and higher terminal latency index of the median nerve.

Due to the mixed results from these studies, as well as the known risk of acute worsening of neuropathic symptoms with single-agent rituximab in the context of an IgM flare, other therapies have been explored [19, 20]. A retrospective study of 45 patients receiving chemoimmunotherapy suggested additional clinical improvement beyond single-agent rituximab [24]. In this series, 19 patients received rituximab in combination with chemotherapy (8 cyclophosphamide, 7 fludarabine, and 4 fludarabine with cyclophosphamide), and 16 patients (84%) had improvement in neuropathic symptoms, 2 (10%) remained stable, and 1 (5%) had worsening neuropathy with a median time to response of 5 months. The added neurologic benefit of combination therapy needs to be weighed against the added immunosuppression and other toxicities related to chemotherapy. The Bruton tyrosine kinase (BTK) inhibitor ibrutinib was investigated in three patients with anti-MAG neuropathy and WM with *MYD88 L265P* mutation [25]. In this series, the INCAT disability score, INCAT sensory score, Medical Research Council sum score, and modified International Cooperative Ataxia Rating Scale were used to assess neuropathy. Patients with at least 1 point improvement in 2 clinical scales were labeled as responders. All three patients reported early subjective improvement in symptoms, and objective improvement was also noted. Based on these data and the potential efficacy of rituximab in patients with anti-MAG PN, a single-arm phase 2 clinical trial was developed to investigate using rituximab and the second-generation BTK inhibitor acalabrutinib (NCT05065554). Preliminary data from this trial have shown that 4 out of 7 (57%) evaluable patients had improvement on the Inflammatory neuropathy Rasch-built Overall Disability Scale (I-RODS) neurologic assessment tool [26].

In patients without an anti-MAG antibody, testing antibodies against gangliosides GM1, GM2, GD1a, GD1b, GQ1b, and asialo-GM1, as well as sulphate-3-glucoronyl paragloboside (SGPG) antibodies, can be considered. It has been shown that approximately 35% of patients with an IgM monoclonal paraprotein and without an anti-MAG will have anti-ganglioside antibodies and 9% an antibody against ganglioside complexes [27, 28]. Anti-ganglioside antibody activity is generally associated with motor neuropathy [16]. The best treatment in these cases is unclear, as rituximab has not shown to be effective in some cases with high titer anti-ganglioside antibodies [29].

AL Amyloidosis

AL amyloidosis is a life-threatening disorder characterized by a clonal plasmacytic or lymphoplasmacytic population of cells in the bone marrow. These clonal cells are the source of an unstable immunoglobulin that misfolds, forms fibrils, and deposits in organs, causing dysfunction in multiple organs, including the heart, kidneys, nerves, lungs, liver, and gastrointestinal tract [30]. Typically, the unstable immunoglobulin fragment in AL amyloidosis is a lambda light chain, although in approximately 25% of cases the unstable protein is a kappa light chain, and in rare cases the amyloidogenic protein may be a heavy chain, as in heavy chain (AH) amyloidosis or light/heavy chain (ALH) amyloidosis [31]. In approximately 7% of AL amyloidosis cases there is an underlying IgM paraprotein [32]. Patients with an IgM-associated AL amyloidosis typically present at an older age, with higher rates of renal, neurologic, lymph node, and lung involvement and lower rates of cardiac involvement compared with those patients that have non-IgM AL amyloidosis [13, 32–38].

In patients with monoclonal gammopathy, there is a 2.9-fold increased risk of developing AL amyloidosis if neuropathy is present compared to those with no neuropathy [6]. These patients typically progress to AL amyloidosis within a year of MGUS diagnosis, highlighting the importance of evaluating all patients with newly diagnosed MGUS for amyloidosis.

Approximately 17–35% of patients with AL amyloidosis have PN, with the highest rates in those patients with IgM-associated amyloidosis, though it is not the presenting symptom in most patients and is often discovered incidentally after an amyloidosis diagnosis is made [39–41]. The PN in amyloidosis is generally length-dependent, symmetric, and progressive. Small-fiber sensory and autonomic functions are affected first, often leading to prominent neuropathic pain and symptoms of autonomic dysfunction, including early satiety, diarrhea or constipation, erectile dysfunction, and postural hypotension [41]. Large-fiber sensory and motor nerve fiber dysfunction can also occur, especially as the neuropathy progresses, leading to paresthesias, muscle weakness, and numbness in the extremities [41, 42]. NCS/EMG typically demonstrates axonal sensorimotor polyneuropathy. Carpal tunnel syndrome symptoms also occur in about 21% of patients [40].

Treatment of AL amyloidosis is directed at the underlying clonal plasma or lymphoplasmacytic cells. In most patients with an associated plasma cell dyscrasia, first-line treatment options include high-dose melphalan with autologous stem cell transplantation (HDM/SCT) or daratumumab, cyclophosphamide, bortezomib and dexamethasone (Dara-CYBORD) depending on the functional status, organ function, and disease characteristics of each patient [43, 44]. In patients with IgM-related AL amyloidosis and an underlying lymphoplasmacytic clone, the treatments follow those used for treating WM, such as rituximab and bendamustine [45, 46]. High dose melphalan and autologous stem cell transplantation can also be considered as first-line or consolidative therapy [46, 47]. Based on higher toxicity rates and suboptimal responses reported with ibrutinib, BTK inhibitors are not recommended as first-line treatment for IgM-related AL amyloidosis [48].

POEMS

POEMS is a paraneoplastic syndrome associated with an underlying plasma cell clone. Polyneuropathy, organomegaly, endocrinopathy, monoclonal protein, and skin changes are the most common clinical characteristics, but additional features are often present [49]. Diagnosis of POEMS requires the presence of a polyneuropathy, which is typically demyelinating, and a monoclonal plasma cell clone that is almost always lambda-restricted and more commonly associated with IgA or IgG rather than IgM. One additional major criterion of Castleman disease, sclerotic bone lesions, or vascular endothelial growth factor (VEGF) elevation and one minor criterion are required to confirm the diagnosis [50]. The minor criteria include organomegaly, extravascular volume overload, endocrinopathy, skin changes, papilledema, and thrombocytosis/polycythemia. The neurologic workup in POEMS should include a detailed history, physical exam, and NCS/EMG. The neuropathy in

POEMS is typically motor-predominant but with sensory symptoms. NCS/EMG typically demonstrates demyelination but with more significant associated axonal loss than other demyelinating neuropathies such as chronic inflammatory demyelinating polyneuropathy (CIDP) [51].

In cases of POEMS with an isolated bone lesion without diffuse marrow involvement, radiation to the bone lesion is recommended. This approach can lead to disease control or often a cure, as demonstrated by a 4-year overall survival of 97% and a 4-year failure-free survival rate of 52% [52]. For the majority of patients who present with disseminated marrow involvement, systemic therapy is indicated, often using alkylator therapy followed by autologous stem cell transplantation. The immunomodulators pomalidomide and lenalidomide, as well as the proteasome inhibitor bortezomib, have shown promising results. Systemic therapy can lead to improvement in the neurologic symptoms.

CANOMAD

Some patients with an IgM paraprotein and neuropathy but without anti-MAG antibodies may have other identifiable autoantibodies [27, 28]. The specificity of these antibodies and the testing yield is highest when specific clinical phenotypes are recognized. CANOMAD, for example, is a rare neurologic syndrome seen in patients with an IgM paraprotein characterized by the combination of unique neurologic findings and key laboratory findings, including IgM autoantibodies targeting gangliosides found on peripheral nerves [53]. The gangliosides most frequently affected by these antibodies are GD1b, GD3, GT1b, and GQ1b, enriched on nerve fibers in the dorsal root ganglia and the oculomotor nerves [54]. These patients also have detectable cold agglutinins in 34–50% of cases [53, 55]. The PN in CANOMAD is a distally predominant sensory neuropathy typically associated with sensory ataxia (76%). Identifying unique features not typical of PN, including ophthalmoplegia leading to diplopia (45%) or bulbar symptoms (13%), are an important clue to this rare diagnosis and should prompt testing for the relevant gangliosides. NCS/EMG may reveal demyelination, axonal features, or both.

One-third of patients with CANOMAD have an underlying hematologic malignancy, with WM being the most common malignancy, but diffuse large B-cell lymphoma, monoclonal B-cell lymphocytosis, chronic lymphocytic leukemia, marginal zone lymphoma, or mantle cell lymphoma may also be present [55]. Due to the rarity of this condition, only observational studies are available to guide treatment. Proposed regimens include plasma exchange, intravenous immunoglobulin (IVIG), rituximab, or a combination of rituximab and IVIG [55–61]. Steroids and immunosuppressive agents are thought to be largely ineffective. IVIG is proposed as the first line of therapy, with success rates ranging from 50–69% in retrospective studies. Rituximab is recommended in the absence of clinical response or cases of early relapses during IVIG tapering or less than 2 years after IVIG therapy [55, 62]. There is a case report demonstrating the success of daratumumab in a patient with CANOMAD that was refractory to rituximab, IVIG, steroids, and ibrutinib [63].

Multifocal Motor Neuropathy (MMN)

Other autoimmune phenotypes of neuropathy have been associated with paraproteinemia, some of which are associated with a readily identifiable serologic marker while others are not. MMN can be seen in patients with IgM monoclonal gammopathy and is classically associated with IgM autoantibodies against GM1 ganglioside [64]. Patients present with asymmetric, distally predominant, slowly progressive weakness and atrophy without sensory loss, usually affecting the arms more so than the legs. Comorbid monoclonal gammopathy is also common among patients with CIDP and variants [65]. These patients typically present with proximal and distal weakness, sensory loss, and demyelination seen on NCS/EMG. Identifying this syndrome is especially important because affected patients can respond to traditional immunotherapy such as IVIG.

Cryoglobulinemia

Cryoglobulinemia is an immune complex deposition disease typically resulting in systemic vasculitis. It is classified into multiple types, with Type 1 including only a monoclonal gammopathy and Type 2 including a monoclonal and polyclonal gammopathy [66]. Type 1 and 2 cryoglobulinemia are associated with a monoclonal gammopathy or a B-cell malignancy in 40 and 60% of patients, respectively. Type 2 cryoglobulinemia is typically associated with hepatitis C, but in less than 10% of cases, a B-cell malignancy is also present. PN occurs in 60–70% of patients with cryoglobulinemic vasculitis but can occur without systemic vasculitis [67]. The neuropathy associated with cryoglobulinemia typically presents with pain, weakness, and sensory deficits [67]. While usually distally predominant, it is very often asymmetric; it may also present as mononeuropathy multiplex, with discrete involvement of multiple identifiable single peripheral nerves [68]. The sensory loss usually involves large and small fibers. Electrodiagnostic tests typically reveal an axonal sensorimotor polyneuropathy. Treatment in these cases is generally directed at the specific underlying B-cell disorder.

Diagnostic Approach in Clinical Practice

The workup performed on a patient with concomitant peripheral neuropathy and a monoclonal paraprotein should characterize the neuropathy, determine the relationship between the neuropathy and the paraprotein, and assess the impact of the neuropathy on the patient's activities of daily living (ADLs). As part of the initial evaluation, other common causes of peripheral neuropathy should be ruled out, including diabetes, vitamin B12 deficiency, alcohol use, prior chemotherapy exposure, chronic infection (e.g., HIV), and thyroid dysfunction. The bedside neurologic examination can also provide clues to important mimics; asymmetry of sensory loss, weakness, or reflex loss could indicate radiculopathy from structural spine disease, while hyperreflexia can indicate myelopathy. Ideally, we recommend an evaluation by a neurologist specializing in neuropathy since defining the clinical phenotype of neuropathy is critical in recognizing the classic paraprotein-associated neuropathies described above.

NCS/EMG is typically indicated to determine if the patient has axonal or demyelinating neuropathy. Anti-MAG neuropathy and POEMS, for example, are expected to have demyelinating features. VEGF, anti-MAG, cryoglobulins, and anti-ganglioside antibody testing can be sent depending on the clinical picture. As a reminder, recognizing multi-organ system involvement may be the key to identifying specific neuropathy syndromes (e.g., AL amyloidosis and cryoglobulinemia), so additional testing (e.g., kidney function, cardiac assessments) may be indicated based on the clinical scenario.

When one of the classic disease entities described above (e.g., anti-MAG neuropathy) is identified, a link between the neuropathy and the paraprotein can be safely assumed (Table 1). However, a clear relationship between the PN and the underlying paraprotein cannot be established through clinical and laboratory testing alone. This situation is most common in cases of IgG or IgA monoclonal gammopathy concurrent with an axonal PN or in patients with an isolated small fiber neuropathy. Pathologic evidence can sometimes provide a link [69]. When AL amyloidosis is clinically suspected, pathological confirmation is required. An abdominal fat pad biopsy or aspirate can be done initially, with plans for additional direct organ biopsy (such as sural nerve or other involved organ) later if clinical suspicion remains high despite an unremarkable fat pad biopsy.

Sural nerve biopsies in patients with WM and anti-MAG antibodies demonstrate IgM deposits on the myelin sheath, demyelination, and widened myelin lamellae [10]. While not clinically necessary when anti-MAG antibodies and typical NCS/EMG findings are found, occasionally, these findings can be helpful when the clinical or electrodiagnostic picture is unclear. Patients with PN and IgM monoclonal gammopathy without anti-MAG antibodies have been found to have endoneurial deposits of the monoclonal protein in patterns distinct from amyloidosis or cryoglobulinemia, which may suggest other pathologic mechanisms are possible [10, 70–72]. Case reports have also demonstrated immunoglobulin deposition along the perineurium or myelin sheath in the sural nerve [73]. Occasionally, nerve biopsy may detect direct invasion of nerves by malignant cells (i.e., neurolymphomatosis). These patients typically present with patchy, asymmetric PN and significant neuropathic pain.

Sural nerve biopsies carry risks, such as infection, delayed wound healing, and permanent paresthesia, dysesthesia, or pain, which can occur in up to 40% of patients [74, 75]. They are not indicated in every patient with PN and monoclonal gammopathy. To avoid the morbidity of a sural nerve biopsy, we and others have explored the potential of skin biopsies to evaluate for paraprotein deposition. Skin biopsies can identify amyloid deposition or IgM deposition [76]. A fourteen-patient case series described the findings of IgM deposits on dermal myelinated fibers in patients with anti-MAG neuropathy, which was more prevalent in the distal lower extremity [77]. Another case series of twelve patients revealed IgM deposits within perineurium-enclosed nerves with a correlation of IgM deposition with the serum IgM level but not the anti-MAG titer [78]. Another case series of 136 patients with either WM or an IgM monoclonal gammopathy demonstrated evidence of monoclonal paraprotein deposition on skin punch biopsies in 53 (39%) of patients [79]. Findings on these biopsies varied, including paraprotein deposition in the dermis, nerves, or vasculature and accumulation of lymphoplasmacytic cells or amyloidosis. Examples are shown in Fig. 1 The direct correlation between paraprotein deposition and the clinical symptoms in patients in this series and others has yet to be delineated, and additional research is required. Figure 2 presents a proposed evaluation algorithm for patients with concurrent IgM monoclonal gammopathy and neuropathy.

Treatment Approach in Clinical Practice

An essential component of the initial workup in patients with isolated neuropathy is understanding the impact of neuropathy on the patient's life. This aspect of the care of patients with concurrent IgM monoclonal gammopathy and neuropathy is challenging, as the intensity of the symptoms varies greatly between patients, and there is no standardized tool to establish the need for therapy. In some practices, the Rankin scale is used (Table 2), and treatment initiation is

Table 1 Common Neuropathic Entities Associated with Monoclonal Gammopathy

Disease Entity	Neuropathy Characteristics	Other systemic Features	Key Laboratory Findings	Electrodiagnostic Findings	Potential treatments
Anti-MAG neuropathy	Slowly progressive, symmetric, distally predominant sensorimotor neuropathy Cranial nerve involvement, autonomic dysfunction, and proximal muscle weakness are rare	N/A	IgM gammopathy on SIFE Elevated anti-MAG titers (typically > 70,000 Buhlmann units)	Demyelinating neuropathy with disproportionate prolongation of distal motor latencies Features of secondary axonal degeneration may be present	Rituximab single-agent Rituximab with chemotherapy BTK inhibitor
AL Amyloidosis	Length-dependent, symmetric, and progressive Small-fiber sensory and autonomic functions (GI motility, erectile function, orthostasis) are often affected prominently Large-fiber sensory and motor nerve fiber dysfunction can also occur	Cardiac, renal, pulmonary, or liver dysfunction may also occur	Monoclonal gammopathy, most frequently with a lambda restriction Possible lab abnormalities related to other end-organ damage: Albuminuria or elevated troponin, NT-proBNP, alkaline phosphatase, or creatinine	Axonal sensorimotor polyneuropathy	Non-IgM: HDM/SCT or Dara-CYBORD IgM or WM-related: rituximab/bendamustine
Cryoglobulinemia	Distally predominant, often asymmetric May present as mononeuropathy multiplex with involvement of multiple single peripheral nerves Usually involves large and small fibers	Other manifestations of vasculitis such as renal dysfunction, arthralgias, livedo reticularis, or skin ulcers	Positive cryocrit, identified as Type 1 or 2 cryoglobulinemia	Axonal sensorimotor polyneuropathy; often asymmetric May be normal if neuropathy is limited to small fibers	Directed at the specific underlying B-cell disorder
CANOMAD	Distal predominant sensory neuropathy typically associated with sensory ataxia Cranial nerves affected, with ophthalmoplegia leading to diplopia (45%) or bulbar symptoms (13%)	WM, DLBCL, MBL, CLL, MZL, or MCL	IgM Anti-ganglioside abs (GD1b, GD3, GT1b, or GQ1b) Cold agglutinins	Demyelination, axonal features, or both	Plasma exchange, IVIG, rituximab, or a combination of rituximab and IVIG
POEMS	Initially can appear length dependent with sensory and motor features, but develops severe proximal + distal weakness. Can mimic CIDP	Castleman disease, sclerotic bone lesions, organomegaly, extravascular volume overload, endocrinopathy, skin changes, papilledema, or thrombocytosis	Monoclonal gammopathy: Almost always *lambda* restricted, most commonly IgA or IgG Elevated VEGF	Demyelination, but with more significant associated axonal loss than other demyelinating neuropathies such as CIDP	Alkylator therapy followed by autologous stem cell transplantation, immunomodulators, or proteasome inhibitors

MAG, myelin-associated glycoprotein; *SIFE*, serum immunofixation electrophoresis; *VEGF*, vascular endothelial growth factor; *DLBCL*, diffuse large B-cell lymphoma; *MBL*, monoclonal B lymphocytosis; *CLL*, chronic lymphocytic leukemia; *MZL*, marginal zone lymphoma; *MCL*, mantle cell lymphoma; *IVIG*, intravenous immunoglobulin; *HDM/SCT*, high-dose melphalan with autologous stem cell transplantation; *Dara-CYBORD*, daratumumab, cyclophosphamide, bortezomib and dexamethasone; *CIDP*, chronic inflammatory demyelinating polyradiculoneuropathy

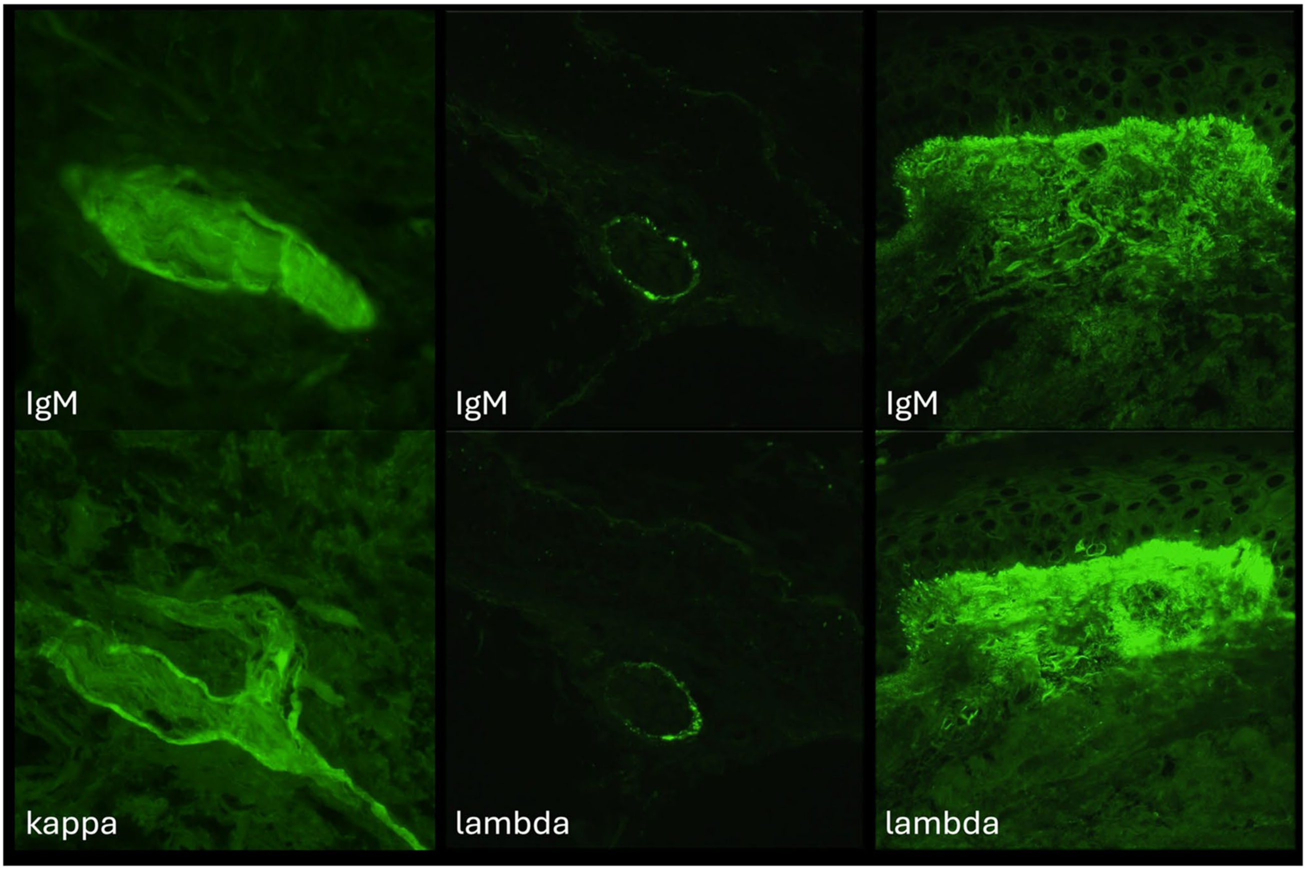

Fig. 1 Immunofluorescence stains showing IgM kappa deposition in skin small nerve fibers (left), IgM lambda deposition in the adventitia of small artery with focal perineural infiltration of the nerves (center), and IgM lambda deposition in the dermis and papillary dermis with diffuse nodular involvement

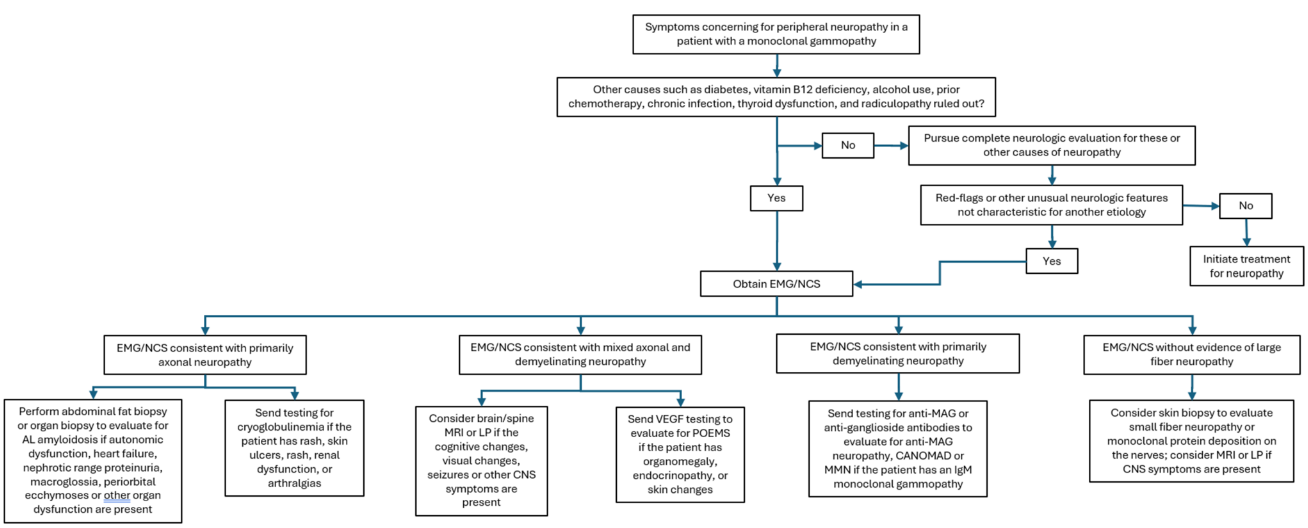

Fig. 2 Schematic decision tree for the evaluation of monoclonal gammopathy-associated peripheral neuropathy. EMG/NCS, electromyography and nerve conduction studies; LP, lumbar puncture; CNS, central nervous system; CANOMAD, Chronic ataxic neuropathy, Ophthalmoplegia, immunoglobulin M paraprotein, Cold agglutinins, and Disialosyl antibodies; MMN, multifocal motor neuropathy; MAG, myelin associated glycoprotein; POEMS, Polyneuropathy, Organomegaly, Endocrinopathy, M-protein, and Skin changes

Table 2 Modified Rankin Scale [80]

Grade	Description
0	No symptoms
1	No significant disability despite symptoms: able to carry out all usual duties and activities
2	Slight disability: unable to carry out all previous activities but able to look after own affairs without assistance
3	Moderate disability: requiring some help, but able to walk without assistance
4	Moderately severe disability: unable to walk without assistance, and unable to attend to own bodily needs without assistance
5	Severe disability: bedridden, incontinent, and requiring constant nursing care and attention

recommended with a Rankin score of 2 or higher. A Rankin score of 1 with progressive symptoms can sometimes indicate pursuing treatment. In those patients with an isolated slowly progressive neuropathy without evidence of other organ involvement, such as that seen with AL amyloidosis and POEMS, in whom the symptoms do not impact ADLs, observation may be considered as the clinical course of neuropathy can be protracted, and symptoms might not progress for years. In those patients with signs of end organ dysfunction, such as renal involvement by AL amyloidosis or bone lesions related to POEMS, will require therapy even in the absence of significant neuropathy.

In those patients in which the paraprotein is unlikely to be the cause of neuropathy, treatment options include ongoing monitoring or an in-depth conversation about the risks and benefits of paraprotein-directed therapy with the patient and healthcare provider, understanding that treatment may not stop or slow the neuropathy progression if the neuropathy is coincident to but not a consequence of the paraprotein.

If a paraprotein-related neuropathy is likely and the symptoms affect the patient's ADLs or other end organ dysfunction is confirmed, treatment of the paraprotein is recommended to achieve a deep hematologic response. Treatment options for IgM-related PN include IVIG, rituximab monotherapy, or regimens used to treat WM as recommended by the National Comprehensive Cancer Network and the International Workshop for WM as mentioned previously. In our practice, we prefer to treat patients with anti-MAG neuropathy with a combination chemoimmunotherapy (e.g., bendamustine and rituximab) or BTK inhibitors (e.g., zanubrutinib) over rituximab monotherapy or IVIG, given the higher rates of deep response seen with the former regimens. If available, patients should be considered for clinical trial participation.

Conclusion

It is essential to consider that neurologic responses can take months to years after therapy administration, so the success of therapy even in those cases with a clear connection between the monoclonal protein and the neuropathy, may be challenging to understand. There is no validated tool to assess neurological response in IgM neuropathy, and the criteria for treatment re-initiation are not well defined. Due to these challenges it is important that the care of patients with concurrent IgM gammopathy and neuropathy include a hematologist/oncologist and a neurologist with comprehensive knowledge of these distinct entities. Furthermore, practitioners involved in the care of these patients should continue to offer clinical trials as available in an effort to improve care for future patietns with monoclonal gammopathy and neuropathy.

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Data Availability No datasets were generated or analysed during the current study.

Declarations

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Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

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