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Paraproteinemic neuropathy

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Paraproteinemia is caused by a proliferation of monoclonal plasma cells or B lymphocytes. Approximately 10% of idiopathic neuropathies are associated with paraproteinemia, where a certain paraprotein acts like an antibody targeted at constituents of myelin or axolemma in peripheral nerves. The relationship between paraproteinemia and peripheral neuropathy remains unclear despite this being of interest for a long time. Neurologists frequently find paraproteinemia during laboratory examinations of patients presenting with peripheral neuropathy, especially in the elderly. The possibility of a relationship with paraproteinemia should be considered in cases without an explainable cause. We review the causal association between paraproteinemia and neuropathy as well as clinical, laboratory, and electrophysiologic features, and the treatment options for paraproteinemic neuropathy.

Key words: Monoclonal gammopathy; Paraproteins; Peripheral neuropathy; POEMS Syndrome; Multiple myeloma; Waldenstrom macroglobulinemia

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INTRODUCTION

A paraprotein is an anomalous blood immunoglobulin (Ig; usually monoclonal, termed an M-protein or M-spike) that is produced in excess by the abnormal clonal proliferation of monoclonal plasma cells or B-lymphocytes (monoclonal gammopathy), and it comprises a heavy chain (IgG, IgM, and IgA) and a light chain (kappa or lambda). Paraproteinemia constitutes a heterogeneous group of disorders ranging from preclinical monoclonal gammopathy of unknown significance (MGUS), to hematologic malignant disorders such as multiple myeloma (MM), POEMS syndrome (comprising polyneuropathy, organomegaly, endocrinopathy, M-protein, and skin changes), Waldenström macroglobulinemia (WM), and amyloidosis (AL). Paraproteinemic neuropathy refers to neuropathy associated with a paraprotein or monoclonal gammopathy.

Here we address neuropathy associated with paraproteinemia to answer whether there are distinctive clinical, laboratory, or electrophysiologic features, and provide treatment recommendations.

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EPIDEMIOLOGY

The prevalence of monoclonal gammopathy is approximately 1% in those older than 50 years, and increases to approximately 3% in those older than 70 years.[1] Up to 10% of cases of idiopathic neuropathy are associated with monoclonal gammopathy, which is six- to tenfold higher than the prevalence in the general population.[2] The most common paraprotein in patients with peripheral neuropathy is IgM, which is frequently found in MGUS or WM,[3] while IgG is usually associated with MM, POEMS syndrome, or AL. About 30% of the patients with paraproteinemia who present with peripheral neuropathy have MM, POEMS syndrome, AL, lymphoma, or another plasma cell disorder, while the remainder have MGUS.[4]

TESTING FOR PARAPROTEINEMIC NEUROPATHY

Paraproteinemia should always be considered in the diagnostic evaluation of a patient with unexplained peripheral neuropathy.[5] Although serum protein electrophoresis is the first step for detecting paraproteinemia, serum immunoelectrophoresis or immunofixation—which is more sensitive for detecting lower levels of monoclonal proteins—is recommended for demarcating the heavy- and light-chain types when the findings of serum protein electrophoresis are normal.[6,7] When paraproteinemia is identified, the amount of the paraprotein should be measured and the type of Ig defined in both the serum and 24-hour urine samples. Laboratory results for the full blood cell count, liver and kidney function tests, serum calcium and phosphate levels, and the erythrocyte sedimentation rate should also be acquired. Patients with a paraprotein should be further evaluated for systemic signs of malignant plasma cell disorder by performing a skeletal survey for any lytic or sclerotic lesions, and computed tomography scans of the chest, abdomen, and pelvis.[5,8] Vascular endothelial growth factor (VEGF) levels should be checked in patients with suspected POEMS syndrome. A bone marrow examination or bone scan is usually performed in patients with an M-protein level of >15 g/L, although some hematologists will perform one of these investigations in all patients with paraproteinemia.[9] The recommended investigations for patients with suspected paraproteinemic neuropathy are summarized in Table 1.

CHARACTERISTICS OF THE UNDERLYING PARAPROTEINEMIC NEUROPATHY

The clinical presentation of paraproteinemic neuropathy varies depending on the underlying paraproteinemic disorders. Table 2 summarizes the clinical, laboratory, and electrophysiologic features as well as the treatment options for each disease entity.

Neuropathy associated with MGUS

Approximately two-thirds of paraproteinemia cases are MGUS.[4] MGUS is a benign condition, and it should satisfy the following criteria: (1) monoclonal protein level <30 g/L, (2) <10% of plasma cells in the bone marrow, (3) no or only a low level of monoclonal protein in the urine, and (4) no end-organ damage (hypercalcemia, renal insufficiency, anemia, or bone lesion).[10] Approximately 1% of patients with MGUS transform into symptomatic plasma cell disorders annually.[11] An initial paraprotein or M-protein concentration of >15 g/L, the detection of an IgM or IgA paraprotein, and an abnormal free-light-chain ratio (free kappa/lambda ratio; normal range = 0.26–1.65) are related to an increased risk of a malignant evolution.[8,12] In patients with MGUS presenting with peripheral neuropathy, progressive weight loss, progression of the neuropathy, and an M-protein level of >1 g/L also have been identified as independent predictors for a malignant transformation.[13,14] Therefore, careful monitoring of Ig levels with regular checkups for any significant changes in clinical symptoms are essential. About one-third of MGUS patients exhibit peripheral neuropathy. Although IgG is the most common paraprotein, IgM is most frequently associated with peripheral neuropathy. IgM (60% of cases) is the monoclonal antibody most likely to react with a neural component, while the least likely is IgA (10% of cases).[15] In addition to the nature of the Ig abnormality, the predominant pattern (axonal vs. demyelinating) in an electrophysiologic study may be helpful for differentiating clinical characteristics and treatment responses in patients with MGUS presenting with neuropathy.

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IgM MGUS

While some patients combining neuropathy with IgM MGUS present with proximal and distal sensorimotor symptoms resembling classic chronic inflammatory demyelinating polyneuropathy (CIDP), others present with a distal-predominant polyneuropathy. The latter group has been classified as distal acquired demyelinating symmetric neuropathy.[16] Almost 50% of patients with peripheral neuropathy associated with IgM paraproteinemia exhibit high titers of anti-myelin-associated glycoprotein (MAG) or one of its sulfated glycolipid derivative (sulfate-3-glucuronyl paragloboside (SGPG) or sulfate-3-glucuronyl lactosaminyl paragloboside (SGLPG)) antibodies that are found in the periaxonal membrane, Schmidt-Lanterman incisures, and paranodal loops.[17,18] Roughly 80% of patients with anti-MAG antibodies have IgM MGUS, and most of the others have WM.[19] The anti-MAG antibody neuropathy presents with a typical pattern of demyelinating neuropathy. This disease is typically prevalent from the 6th to 9th decades of life,[3,20] and is characterized by a predominantly distal involvement, very

Table 1. Examinations for patients with suspected paraproteinemic neuropathy

Routine workup
Clinically neurologic examination at baseline, and follow-up checks at regular intervals
Electrophysiologic test determines whether the polyneuropathy has an axonal (CMAP/SNAP) or a demyelinating (DML/MNCV/TLI and CB/TD) pattern
Serum protein electrophoresis (with the presence or absence of an M-protein), immunoelectrophoresis, or immunofixation (to demarcate the heavy- and light-chain types of the paraprotein)
Quantitative Ig levels
Serum light-chain quantification, and the detection of Bence-Jones protein (free light chains) in a random urine sample; if positive, 24-h urine collection for urine protein quantification
Full blood cell count with differential, kidney and liver function tests, calcium and phosphate levels, and erythrocyte sedimentation rate
Physical examination for involvement of systemic organs such as lymphadenopathy, hepatosplenomegaly, ascites, edema, or macroglossia
Radiographic X-ray skeletal survey (including the skull, pelvic, spine, and ribs) to look for lytic or sclerotic lesions. If lytic or sclerotic lesions are strongly suspected, CT and/or MRI of the spine, pelvis, or whole body may be considered
Ultrasonography or CT of the chest, abdomen, and pelvis (to detect organomegaly or malignancy)
Bone-marrow aspiration and biopsy (required if the M-protein level is >15 g/L or the free-light-chain ratio is abnormal)
CSF analysis involving cellularity, cytospin, and protein level
Advanced workup
Serum VEGF levels if POEMS syndrome is suspected Anti-MAG antibody[a]
MRI of nerve roots and brachial plexus, as for CIDP
Nerve biopsy[b]
Fat biopsy, most often when there is suspicion of amyloidosis

General ideas were derived from "Rajabally[22]" and "Rison et al.[99]".

CMAP, compound motor action potential; SNAP, sensory nerve action potential; DML, distal motor latency; MNCV, motor nerve conduction velocity; TLI, terminal latency index; CB, conduction block; TD, temporal dispersion; Ig, immunoglobulin; CT, computed tomography; MRI, magnetic resonance imaging; CSF, cerebrospinal fluid; VEGF, vascular endothelial growth factor; POEMS syndrome, polyneuropathy, organomegaly, endocrinopathy, M-protein, and skin changes; MAG, myelin-associated glycoprotein; CIDP, chronic inflammatory demyelinating polyneuropathy.

[a]Half of patients with IgM paraproteinemic neuropathy have anti-MAG antibodies.

[b]The following conditions are suspected: (1) IgM paraproteinemic demyelinating neuropathy with negativity for anti-MAG antibodies, or IgG or IgA paraproteinemic demyelinating neuropathy with a chronic progressive course, and with the discovery of widely spaced myelin on electron microscopy or deposits of Ig and/or complement bound to myelin; (2) amyloidosis; and (3) malignant lymphoproliferative infiltration of nerves.

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Table 2. Summary of incidence rates, clinical, laboratory, electrophysiologic, and pathologic findings, and treatment options for patients with paraproteinemic neuropathies

Disease	Prevalence of peripheral neuropathy	Clinical	Laboratory	Electrophysiology	Pathology	Treatment
MGUS	30%	Slowly progressive, distal sensory ataxia (IgM); Distal and proximal sensorimotor neuropathy as in CIDP-like neuropathy (IgG/IgA)	M-protein <30 g/L Increased IgM, IgG, or IgA level Anti-MAG antibodies detection in half (IgM)	Demyelinating with remarkably prolonged distal latencies Reduced TLI (IgM) CIDP-like or axonal (IgG/IgA)	Widening of myelin lamellae IgM antibodies against MAG, gangliosides (anti-GM1, -GD1a, -GD1b, or -GM2), sulfatide, chondroitin sulfate C Endoneurial Ig deposits	IgM MGUS (especially anti-MAG neuropathy) IVIg Interferon alfa-2a Plasma exchange Rituximab + Cyclophosphamide + steroid IgG/IgA MGUS IVIg Corticosteroid Cyclophosphamide + steroid Plasma exchange
Multiple myeloma	10–75% (throughout disease course)	Length-dependent sensory or sensorimotor neuropathy	M-protein >30 g/L Bence-Jones proteinuria >10% plasma cells in bone marrow IgG (50%) or IgA (20%) kappa Anemia, hypercalcemia	Almost always axonal	Axonal degeneration with or without amyloid deposition	No intervention reverses neuropathy; treating myeloma can cause or exacerbate existing neuropathy
POEMS syndrome	50–85% (throughout disease course)	Ascending symmetric proximal and distal sensorimotor symptoms (CIDP-like neuropathy) Weakness eventually predominant	IgG or IgA lambda Elevated VEGF Sclerotic bone lesions	Mixed demyelinating and axonal No conduction block or temporal dispersion Normal TLI	Axonal degeneration Loss of myelinated fibers Inflammation in endoneurium, and uncompacted myelin lamellae	Isolated bone lesion without clonal plasma cells Radiation Disseminated bone-marrow involvement Corticosteroids Melphalan + dexamethasone Cyclophosphamide + dexamethasone Auto-PBSCT Thalidomide or lenalidomide + dexamethasone Bortezomib Bevacizumab

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Table 2. Continued

Disease	Prevalence of peripheral neuropathy	Clinical	Laboratory	Electrophysiology	Pathology	Treatment
Waldenström macroglobulinemia	10–47% (throughout disease course)	Slowly progressive symmetric distal sensory, or sensorimotor (CIDP-like neuropathy) symptoms	IgM kappa Anti-MAG antibodies in some cases	Similar to IgM MGUS	Similar to IgM MGUS	Primary Rituximab + cyclophosphamide + dexamethasone + fludarabine Refractory Bortezomib, rituximab, autologous stem-cell transplantation Weekly plasma exchange
Amyloidosis	Presenting symptom is neuropathy in 15–30%	Painful progressive symmetric, distal sensorimotor with or without dysautonomia Carpal tunnel syndrome in 25%	IgG or IgA lambda Occurs alone or with other plasma-cell disorders	Axonal sensorimotor neuropathy Carpal tunnel syndrome	Endoneurial amyloid deposition on Congo-red staining Light chains on immunochemistry Axonal degeneration	If eligible, autologous stem-cell transplantation If not eligible, melphalan, corticosteroid thalidomide, lenalidomide, and bortezomib

General ideas were derived from "Raheja et al.[8]" and "Rison et al.[99]".

MGUS, monoclonal gammopathy of undetermined significance; IgM, immunoglobulin M; IgG, immunoglobulin G; IgA, immunoglobulin A; MAG, myelin-associated glycoprotein; TLI, terminal latency index; GM, ganglioside M; GD, ganglioside D; IVIg, intravenous immunoglobulin; CIDP, chronic inflammatory demyelinating polyneuropathy; POEMS syndrome, polyneuropathy, organomegaly, endocrinopathy, M-protein, and skin changes; VEGF, vascular endothelial growth factor; Auto-PBSCT, autologous peripheral-blood stem-cell transplantation.

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slow progression, prominent sensory involvement, but little or no weakness.[21,22] Most of these patients have a favorable prognosis with little functional deterioration over time, but the neuropathy can progress rapidly during certain stages.[23]

The anti-MAG antibody neuropathies show absent or remarkably reduced sensory nerve action potentials that are indicative of axonal damage in diffuse nerves of the lower limbs.[22,24,25] Motor nerve conduction studies show greatly prolonged distal motor latencies suggestive of distal-dominant demyelination. A terminal latency index (TLI = distal distance/[forearm motor conduction velocity × distal motor latency]) of <0.26 is highly specific for anti-MAG antibody neuropathy with a demyelinating pattern.[16,22] The TLI has previously been found to be considerably lower in anti-MAG antibody neuropathy than in other demyelinating neuropathies such as CIDP and Charcot Marie-Tooth neuropathy type 1a.[26,27] This characteristic feature means that an electrophysiologic test is a suitable first step for distinguishing anti-MAG antibody neuropathy from the other demyelinating neuropathies. The pathomechanism underlying this combination of both diffuse axonal loss and distal demyelination, which is not common in CIDP, is unclear. In contrast to CIDP, conduction block and abnormal temporal dispersion are not present due to the demyelination exclusively dominating the distal region. It has been hypothesized that distal nerve fibers are more vulnerable to anti-MAG antibodies due either to greater permeability of the blood–nerve barrier or more-prominent MAG expression.[25,28] In addition, the anti-MAG antibody impairs neurofilament phosphorylation, resulting in neurofilament accumulation followed by disturbed axonal transport in neurons, which in turn may induce axonal degeneration in more-distal regions of the longer axis.[25,29]

The decision to attempt treatment should be made depending on the severity of the objective clinical manifestation. There is currently insufficient evidence of a clinical benefit of immunotherapies in patients with anti-MAG antibody neuropathy. We identified only 7 small randomized controlled trials (RCTs) involving 182 participants that have tested the efficacies of intravenous Ig (IVIg), interferon alfa-2a, plasma exchange, cyclophosphamide and steroid, and rituximab. IVIg showed a small effect from a functional perspective in a small double-blind RCT that did not include patients with anti-MAG reactivity, and also in an open-label study.[22,30] Only 2 trials of IVIg involving 33 participants (including 20 patients with anti-MAG antibodies) found short-term benefits (at 4 weeks) in the Neuropathy Impairment Score (NIS), the modified Rankin Scale (mRS) score, and the 10-meter walk time, and also relative safety.[31,32] Two RCTs of interferon alfa-2a produced conflicting results: interferon alfa-2a showed some benefit in treating anti-MAG antibody neuropathy in assessments using the NIS at 6 months in an open trial with IVIg,[32,33] while a double-blind placebo-controlled study found that interferon alfa-2a provided no significant benefit in both the NIS and mRS score at 6 months.[34] Plasma exchanges also exerted temporary effects in about 50% of patients in uncontrolled studies.[22,23] However, a prospective analysis found no efficacy in most anti-MAG-positive cases, and that the efficacy was no better for plasma exchanges in conjunction with chlorambucil than for chlorambucil alone (based on the NIS at 4 months).[22,35] A trial of the efficacy of combined cyclophosphamide and steroid produced some positive findings.[36] Rituximab has recently been investigated in two RCTs,[37,38] and its efficacy in IgM anti-MAG neuropathy has been reported for several cases and small case series.[20,39,40] One of the two RCTs found no significant benefit in using the Inflammatory Neuropathy Course and Treatment disability score of the leg as the primary outcome at 8 months,[37] while the other RCT of polyneuropathy associated with anti-MAG IgM monoclonal gammopathy found no significant efficacy at a 1-year follow-up in 26 patients with rituximab (4 weekly infusions of 375 mg/m^2) compared to 28 patients in the placebo group. A recent follow-up study also found no significant improvement.[38] Corticosteroid was not effective when used as a monotherapy, but it may be beneficial if applied in conjunction with other immunotherapeutic drugs such as cyclophosphamide.[8] Another RCT found no significant improvements in functional scales including the mRS.[36]

IgM-MGUS-associated neuropathy may exhibit the typical pattern of CIDP. Patients with CIDP-like neuropathy associated with MGUS should receive the same treatment as patients with classical CIDP, but continuing treatment as in patients with CIDP is not always needed because a significant proportion of the former patients are stable without treatment.[22]

IgG and IgA MGUS

The association of IgG and IgA paraproteins with neuropathy is not as significant as for IgM. Most patients with neuropathy who have IgG paraproteinemia present with IgG

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MGUS;[19] the other disorders include MM, POEMS syndrome, AL, and lymphoma. Heterogeneous neuropathies are related to IgG and IgA paraproteinemia. One pattern involves chronic progressive or relapsing demyelinating polyneuropathy, but the onset is frequently subacute, mostly occurring in middle-aged patients. This appears with moderate-to-severe weakness but a relatively good response to immunosuppressants, which suggests a dysimmune pathogenesis. Another pattern is a chronic slowly progressive distal-predominant sensory axonopathy occurring in older patients.[41] The symptoms are usually mild, but the response to immunosuppressants is poor. These findings are consistent with those reported previously for other series.[42–44]

The mechanism underlying peripheral neuropathy is unclear.[45] Direct deposition of IgG or IgA has rarely been detected in peripheral nerves.[41,43,46] Occurrence in the elderly, which is the most common age group for the development of peripheral neuropathy, and the high prevalence of IgG paraproteins of up to 3% after the age of 70 years may support a coincidental association between neuropathy and IgG paraproteinemia.[43] However, the more frequent occurrences of antineural neurofilament, glycoprotein, or glycolipid antibodies, including tubulin, SGPG, and MAG, and antibodies to GM1, sulfatide, or chondroitin sulfate C have been observed in only a minority of patients with axonal neuropathy associated with MGUS, in contrast to those without MGUS.[43,45,46] Therefore, IgG or IgA MGUS may be a secondary marker of nerve damage in these patients.

Immunotherapies such as IVIg (at 2.0 g/kg and administered over 2–5 days), plasma exchange (at 200 mL/kg and administered in four or five exchanges), or corticosteroids elicited better responses in patients with IgG or IgA MGUS than in those with IgM MGUS.[18,45,47,48] Plasma exchange typically induced temporary stability or improvement in an RCT with a placebo group.[18] Many patients required periodic treatment repeats. An RCT that compared plasma exchange with sham plasma exchange in 18 participants with IgG or IgA paraproteinemic neuropathy with a 3-week follow-up period found that plasma exchange exhibited modest efficacy in the weakness domain of the NIS and with good safety results: the mean improvement was 17 points in the plasma exchange group compared to 1 point in the sham group. However, there were no statistically significant differences in the overall NIS, vibration thresholds, or neurophysiologic indices.[49,50] Other observations and open trials involving plasma exchange, cyclophosphamide combined with steroid, IVIg, and corticosteroid monotherapy did not produce any significant evidence of treatment efficacy.[41,43,50]

Neuropathy associated with MM

MM secreting a monoclonal protein is a plasma-cell neoplasm of the bone marrow that mostly presents with bone pain (e.g., in the spine, ribs, or hip), tiredness, and repeated infections.[19,51] In nervous-system involvement, compressive radicular pain due to lytic bone lesions, pathologic fractures, and plasmacytoma in the spine are the most common symptoms.[51] The diagnosis of MM is usually based on the following clinical findings: (1) serum M-protein, (2) Bence-Jones proteinuria, (3) increased bone-marrow plasma cells (≥10%), and (4) evidence of end-organ damage, such as hypercalcemia (serum calcium ≥ 11.5 mg/dL), renal insufficiency (serum creatine >1.73 mmol/L), anemia (normochromic, normocytic with a hemoglobin level of >2 g/dL below the lower limit of normal, or a hemoglobin level of <10 g/dL), or osteolytic bone lesions.[8,11] About 50% of patients have an IgG heavy chain, with IgA being the second most common type.[52] Kappa is the most common light chain in MM.[8] Only 10% of patients present neuropathy as a dominant feature, and it commonly precedes the discovery of the plasma cell disorder.[53] Approximately three-quarters of patients suffer from peripheral neuropathy during the course, either as the disease itself by perineurial or perivascular IgG kappa deposition with or without associated amyloid infiltration or as a complication of the treatment agent.[51,54] Patients typically develop mild symmetric sensory symptoms and signs involving all sensory modalities in the distal extremities rather than weakness, and the symptoms are more painful in cases with concurrent amyloid deposition. Also, ankle reflexes may be decreased or absent.[3]

Electrophysiologic studies usually show axonal features of mild slowing of motor conduction velocities and low or absent compound muscle action potentials and sensory nerve action potentials.[55–57] Differentiating the neuropathy associated with MM itself from treatment-induced toxic neuropathy is difficult due to the similarity of the clinical and electrophysiologic findings, so a careful neurologic evaluation before treatment is essential when managing these patients.

The primary target for treatment is the MM disease activity

itself, but combined pain should also be considered.[8] Unlike the other types of paraproteinemia, no intervention reverses the peripheral neuropathy associated with MM. Current treatments for MM include autologous stem-cell transplantation and various chemotherapeutic options including thalidomide, bortezomib, lenalidomide, and pomalidomide. Certain chemotherapies can cause or exacerbate existing neuropathy in up to 65% of patients.[8,58] The most common offending medications are bortezomib and thalidomide, which may produce a length-dependent axonal polyneuropathy that is primarily sensory,[8,51,53] while lenalidomide is less neurotoxic.[59] Early recognition of chemotherapy-induced neuropathies is critical for decreasing the probability of permanent neural damage via dosage reduction or discontinuation of the causal agent in patients with a good clinical status.

POEMS syndrome

The synonyms for POEMS syndrome include osteosclerotic myeloma, Crow-Fukase Syndrome, and Takatsuki syndrome. Its diagnosis requires at least three of the major criteria and at least one of the minor criteria to be fulfilled. The major diagnostic criteria are (1) polyneuropathy, (2) clonal plasma-cell dyscrasia (almost always lambda), (3) sclerotic bone lesions or Castleman disease, and (4) increased level of VEGF, with a diagnosis normally requiring both polyneuropathy and clonal plasma cell disorder to be present.[8,60] The minor diagnostic criteria are organomegaly such as hepatosplenomegaly or lymphadenopathy, extravascular volume overload, endocrinopathy, skin changes, papilledema, and thrombocytosis/polycythemia.[61] POEMS syndrome comprises only 5% of myelomas and typically involves IgG or IgA paraproteins, usually at low titers (<2 g/L in 90% of patients), and the light chain is almost exclusively lambda.[3] There is no specific diagnostic tool for POEMS syndrome, and so a detailed examination is required for an appropriate diagnosis if the disease is suspected. The symptoms usually begin in the 4th to 6th decades of life.[8] In approximately 50% of patients, the polyneuropathy is often an initial manifestation and can be misdiagnosed as CIDP.[62] Any patient who is diagnosed with CIDP that is not responding to standard CIDP therapy should be considered as possible POEMS syndrome.[60] The typical symptoms are numbness, tingling, and coldness sensation in the feet with a symmetric pattern followed by weakness, and the course is progressive with a proximal spread.[63]

An electrophysiologic study of POEMS syndrome shows nerve conduction slowing predominantly in intermediate nerve segments (nerve trunk) rather than in the distal nerve terminals, and severe length-dependent axonal loss or conduction abnormalities (attenuation of compound motor action potential amplitudes especially in the lower extremities). Conduction block, which is common in CIDP and a typical feature of segmental demyelination, is rare in POEMS syndrome.[63–66] Relatively uniform demyelination along the nerve rather than multifocal involvement may be responsible for the rarity of conduction block and temporal dispersion in POEMS syndrome.[65] Neuropathologically, a mingling of demyelination and the degeneration of myelinated axons is usually present. Inflammatory infiltrates may be seen predominantly in the endoneurium, accompanied by endoneurial edema without Ig deposition.[8] Additionally, uncompacted myelin lamellae are found.[67] Pathologic findings suggest that POEMS syndrome involves predominantly intermediate nerve segments and nerve trunks due to the VEGF-mediated breakdown of the blood–nerve barrier.[25,68] This finding contrasts with some other immune-mediated neuropathies in which antibodies can easily access distal nerve terminals and nerve roots where the blood–nerve barrier is vulnerable.[25,63] VEGF increases microvascular permeability, damages endothelial cells, and is important in angiogenesis. The level of VEGF, which may a driving factor in the disorder, is diagnostically useful.[22,67]

IVIg, plasma exchange, and steroid are effective therapies for CIDP, while those for POEMS syndrome include radiotherapy, systemic chemotherapy, and autologous stem-cell transplantation.[63] Therefore, an early differential diagnosis is important for early treatment of POEMS syndrome and CIDP. There have been no RCTs of POEMS syndrome, presumably due to the rarity of the disorder.[69] The choice of treatment is based on the number of osteosclerotic lesions as well as the extent of bone-marrow plasma-cell involvement.[51] The involved sites are currently treated using curative doses of radiation or surgical resection for patients with a dominant sclerotic plasmacytoma without clonal plasma cells found in bone-marrow biopsy.[69–71] Patients with diffuse sclerotic lesions or bone marrow involvement should be offered systemic therapy, which can range from chemotherapy to autologous peripheral blood stem cell transplantation.[51,61] Cortico-

steroids may provide temporary symptomatic improvement. Alkylator-based therapy (e.g., melphalan or cyclophosphamide) has been applied the most frequently.[69] A recent prospective study of combined melphalan and dexamethasone found a high efficacy and low toxicity.[62,72] Recent case series have shown that high-dose chemotherapy with autologous peripheral-blood stem-cell transplantation is an effective treatment in terms of improving the peripheral neuropathy and significantly decreasing serum VEGF levels.[69,73,74] Lenalidomide and thalidomide have also been successful, although this is based on a relatively small amount of data.[69,75–77] A few case reports have demonstrated successful treatment with bortezomib, but the associated risk of exacerbating the peripheral neuropathy should be carefully considered.[69,78] Bevacizumab has shown mixed results in experiments involving five patients, with three patients improving but two expiring.[69,79,80]

Neuropathy associated with WM

WM is characterized by an IgM (usually kappa) paraprotein-associated lymphoplasmacytic lymphoma. It can be diagnosed by detecting serum IgM paraprotein and >10% lymphoplasmacytic infiltration in the bone marrow (predominantly with an intertrabecular pattern).[81] WM is a very rare disease, with an annual incidence of 0.38/100,000 persons, and it typically occurs in the 7th decade with 55–70% of cases involving males. The clinical manifestations are organomegaly, increased vascular viscosity, and pancytopenia. The most common presenting symptom is anemia-related fatigue.[51] About 10% of patients present with peripheral neuropathy, which can reportedly appear in up to 47% of patients throughout the course of disease.[8,82] The neuropathy in WM is clinically indistinguishable from that associated with IgM MGUS.[82] The most common symptoms are numbness or pain of the feet and gait ataxia followed by tremor.[51] About 50% of patients with neuropathy have anti-MAG antibodies.[8] Electrophysiologic studies typically show a pattern of demyelination with prolonged terminal latencies, and significantly reduced conduction velocities. Distal-predominant axonal neuropathies have been shown in some cases in the absence of anti-MAG antibodies, but also in other cases with cryoglobulinemia or amyloid infiltration.[8,81,83] Not all newly diagnosed cases of WM require prompt treatment. Approximately 25% of WM patients are asymptomatic at the diagnosis, and 50% of them will not need therapy within 3 years. The Mayo Clinic consensus guidelines recommend rituximab monotherapy for patients with mild progressive IgM associated neuropathies, and combination therapy with cyclophosphamide, rituximab, and dexamethasone for WM with severe constitutional (e.g., night sweats and fatigue) and hematologic (e.g., hyperviscosity syndrome) symptoms.[83] One study found that approximately 90% of patients with WM responded to the combination R-CHOP chemotherapy regimen of cyclophosphamide, doxorubicin, vincristine, and prednisone plus rituximab.[84] Bortezomib produced excellent response rates of 81–96% in the management of relapsed WM.[53,85] A recent review strongly recommended regimens containing rituximab for patients with more aggressive WM-related neuropathy, such as dexamethasone + rituximab + cyclophosphamide, bendamustine + rituximab, fludarabine + rituximab, fludarabine + cyclophosphamide + rituximab, and cladribine + rituximab.[81] Bortezomib has not been routinely recommended as a primary agent except in the relapse form of WM.[86] Autologous stem-cell transplantation reportedly improves the overall and event-free survival rates in both previously treated and untreated patients.[81,87] Recent reviews suggested the use of autologous stem-cell transplantation for relapsed chemosensitive disease (remission duration of <2 years from induction therapy). The response rate was 90%, and the relapse-free survival rate at 3 years was 65%.[81,87,88] Weekly plasmapheresis has been recommended as a palliative therapy for patients with hyperviscosity symptoms.[8]

Neuropathy associated with AL

There are two types of AL disease entities: inherited AL and primary (nonfamilial) AL.[89] About 90% of patients with primary AL have an M-protein in the serum or urine, which usually consists of IgG or IgA combined with a lambda light chain or the light chain alone. AL should be diagnosed only when all four of the following criteria are fulfilled: (1) evidence of systemic organ involvement, (2) pathologic confirmation of amyloid deposition using Congo red staining, (3) light-chain-related amyloid deposition indicated by either immunohistochemical staining or direct sequencing, and (4) monoclonal plasma-cell disorder.[3,89] Primary AL, which is also called Ig light-chain AL, is a multisystem disorder in which insoluble amyloid fibrils are deposited in various organs, re-

sulting in various systemic organ dysfunctions that appear most frequently in the heart, kidney, liver, gastrointestinal tract, and peripheral nerves.[8,90] Patients can present with multiple symptoms, depending on the affected organ. Asthenia and dyspnea are the most common symptoms, followed by cardiac symptoms. The signs include weight loss, macroglossia, and organomegaly.[89] Roughly 17% of patients with AL show symptomatic peripheral neuropathy, and the incidence increases to 35% if preclinical neuropathy is included.[8] Neuropathy-associated AL usually presents as a progressive sensorimotor axonal polyneuropathy beginning in the legs and with a length-dependent pattern.[91] The neuropathy frequently involves autonomic neurons and the development of various dysautonomic symptoms, such as orthostatic hypotension (55% of patients), gastrointestinal (35%; diarrhea, constipation, dysmotility, and postprandial vomiting), secretomotor, and erectile dysfunction in men.[51] Electrophysiologic studies usually show a symmetric, axonal, sensorimotor polyneuropathy with denervation potentials in distal muscles or a focal neuropathy such as carpal tunnel syndrome. In cases with pure small-fiber involvement that conventional nerve conduction and needle electromyography cannot reveal any abnormalities, a quantitative sudomotor axon reflex test, sympathetic skin responses, or skin biopsy for determining the intraepidermal nerve fiber density may be useful.[92] Because thickening of blood vessel walls in epineurial and endoneurial tissue by amyloid deposition is observed frequently, vascular insufficiency is suggested to be the most likely pathomechanism underlying neuropathy. The direct compression of nerve fibers by AL deposition is also suggested, but this is controversial.[8,93] A highly presumptive diagnosis should be applied to AL patients with neuropathy, because the median survival for patients with amyloid neuropathy is only 18–25 months if left untreated.[92] A combined regimen of high-dose melphalan and autologous stem-cell transplantation currently remains an option only for patients with focal disease (20–25% of patients), which results in the 10-year survival rate increasing to 43–53%.[19,94,95] For the remaining patients, trials of chemotherapy regimens that include melphalan, corticosteroids, thalidomide, lenalidomide, and bortezomib should be considered.[96–98]

CONCLUSIONS

Paraproteinemic neuropathy presents with diverse clinical, laboratory, electrophysiologic, and pathologic features and warrants thorough evaluations for underlying hematologic malignancy. A detailed neurologic examination including the entire nervous system is crucial for characterizing the phenotype, and may require various and specific diagnostic tests to be selected on a case-by-case basis. Paraproteinemic neuropathy should be treated by multidisciplinary specializations, including hematology, radiation oncology, surgery, and rehabilitation therapy as well as neurology. A careful monitoring is also essential in determining the treatment response of the neuropathy.

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