Although polyneuropathies associated with IgM and IgG monoclonal gammopathies have been well described, polyneuropathy with IgA monoclonal gammopathy of undetermined significance (MGUS) is less commonly seen and has not been well studied. We reviewed the clinical and electrodiagnostic features of 5 such patients, and the sural nerve biopsy findings in 4 of them. One patient was diabetic, while 4 were free of other diagnoses commonly associated with neuropathy. Clinical presentations were varied. Electrodiagnostic and histological studies ranged from primary demyelination to primary axon loss to a mixed axonal/demyelinating picture. Three patients who were treated appeared to respond to prednisone or intravenous gamma globulin, despite clear clinical, electrodiagnostic, and histological differences. We conclude that the polyneuropathy associated with IgA MGUS is heterogeneous, similar to that in IgM and IgG MGUS. A trial of immunomodulating therapy appears to be warranted in such patients if the neuropathy is sufficiently severe.
Key words: paraproteinemias • monoclonal gammopathy • neuropathy • electromyography • sural nerve

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POLYNEUROPATHY ASSOCIATED WITH IGA MONOCLONAL GAMMOPATHY OF UNDETERMINED SIGNIFICANCE

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Polyneuropathies associated with monoclonal gammopathies are of interest because of the potential relationship between the monoclonal protein and immune-mediated nerve damage. Clues to pathophysiologic mechanisms may come from clinical presentations and electrodiagnostic studies. Many patients have been described in whom polyneuropathy is associated with IgM or IgG monoclonal gammopathy.[9,10,15,16,19–22,25–29] While some such patients have gammopathies of undetermined significance, others have a variety of malignant plasma cell dyscrasias. The associated polyneuropathies are clinically, electrodiagnostically, and histologically heterogeneous; some exhibit primarily axonal features, while others primarily show demyelination. In contrast, descriptions of patients with polyneuropathy and IgA monoclonal gammopathy—particularly IgA monoclonal gammopathy of undetermined significance (MGUS)—are rare. In an attempt to describe such patients more completely, we have reviewed clinical, electrodiagnostic, and sural nerve biopsy data on a group of such patients seen at our institution.

MATERIALS AND METHODS

All patients seen at the University of Michigan Neuromuscular Clinic in the past 5 years who had both a polyneuropathy and an IgA monoclonal gammopathy were identified, and detailed chart reviews were performed. One patient (patient 5) had diabetes mellitus. No patients had systemic cancer, a history of excessive alcohol use, or other disorders (except for diabetes) known to cause neuropathy. All had undergone a comprehensive evaluation to rule out other causes of neuropathy, including physical examination, complete blood count, Westegren sedimentation rate, glucose, glycosylated hemoglobin, glucose tolerance test, electrolytes, BUN, creatinine, liver function tests, thyroid function tests, vitamin B_{12} level, VDRL, and chest X-ray. Monoclonal gammopathies were detected by high-resolution agarose gel serum elec-

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Table 1. Patient population and immunological features.

Patient	Age (y)	Sex	Light chain	Serum IgA level (mg/dL)*	Urine immunoelectrophoresis	Other disease
1	42	F	Lambda	484	Normal	None
2	41	M	Lambda	436	Normal	None
3	65	M	Kappa	1040	Kappa light chains	None
4	70	M	Lambda	622	Normal	None
5	44	M	Lambda	255	Intact IgA lambda monoclonal protein	Type II diabetes

*Normal = 24–386 mg/dL.

trophoresis, immunoglobulin quantification, determination of kappa-to-lambda light chain ratio and, if necessary, immunofixation.[18] Malignant plasma cell dyscrasias were excluded by normal bone marrow biopsies and radiologic skeletal surveys.

Nerve conduction studies and needle electromyography had been performed on all patients. Motor and antidromic sensory nerve conduction studies were performed using standard techniques of supramaximal percutaneous stimulation and surface electrode recording, maintaining skin temperature ≥ 32°C, as previously described.[1] Needle electromyography recordings were performed using standard concentric needle electrodes.

Sural nerve biopsies, received fresh and stretched by adhesion to a piece of cardboard, were divided into three portions. One portion was fixed in 10% formalin, embedded in paraffin, and stained with hematoxylin and eosin, Masson trichrome, and Congo red for light microscopy. A second portion was fixed in Karnowski mixture (2.5% glutaraldehyde, 3% formalin) and postfixed in 1% osmium tetroxide; part of this was embedded in Epon for light and electron microscopy, while part was treated with glycerol, 70% and 100%, for teasing. The third portion of the nerve was frozen in liquid nitrogen and treated with fluorescein-conjugated goat antibodies against human IgA, IgG, IgM, C3, C4, and kappa and lambda light chains for evaluation under fluorescent light.

Each teased fiber was graded by a neuropathologist as showing one of five patterns: (1) normal; (2) myelin irregularity (focal myelin thickening at the node of Ranvier or the internode); (3) segmental demyelination–remyelination; (4) axonal degeneration; or (5) axonal regeneration. The pathologist then generated an overall histological impression of the neuropathy (demyelinating vs. axonal vs. mixed) based on the predominant finding from teased fiber analysis, in conjunction with Epon-embedded light and electron microscopy results.

RESULTS

Of 50 patients seen in our Neuromuscular Clinic with polyneuropathy and monoclonal or biclonal gammopathy of undetermined significance, 5 (10%) had IgA MGUS. Demographic and immunological features are summarized in Table 1, while clinical features appear in Table 2. Serum

Table 2. Clinical features.

Patient	Clinical presentation	Upper and lower limb strength*	Sensory loss
1	Painful upper and lower extremity paresthesias; bilateral foot drop	Upper: P5/D5– Lower: P5–/D3+	Large and small fiber
2	Painful, distal upper and lower extremity paresthesias	Upper: P5/D5 Lower: P5/D5	Small fiber
3	Back and right leg pain; painful distal paresthesias	Upper: P5/D5 Lower: P5/D5	Large fiber
4	Painful sensorimotor mononeuropathy multiplex	Upper: P5/D5 Lower: P5–/D1	Large and small fiber
5	Painful upper and lower extremity paresthesias with gait ataxia	Upper: P5/D5 Lower: P5/D5	Large and small fiber

*MRC scale. P = proximal; D = distal.

IgA levels varied from normal (patient 5) to moderately elevated (patient 3), with most patients having mildly elevated serum IgA levels. Urine immunoelectrophoresis was normal in 3 of the 5 patients. Serum antibodies to myelin associated glycoprotein (MAG) were absent in patients 1 and 3, and were not assessed in the other patients.

The polyneuropathy was discovered incidentally in patient 3, who presented for evaluation of back and leg pain, but who was found on examination and electrodiagnostic studies to have a polyneuropathy. Shortly after initial evaluation, he developed painful, distal paresthesias. All other patients presented with complaints of pain, sensory loss, weakness, or a combination of these. Neurological examination (Table 2) revealed weakness which was predominantly distal in 2 patients, while strength was normal in the others. Sensory loss was present in all. Only patient 1 had total areflexia, though Achilles reflexes were absent in patients 3 and 4.

Electrodiagnostic data for several representative nerves is summarized in Table 3. Patient 1 was felt to have a primary demyelinating polyneuropathy, and was the only subject whose EMG met formal electrodiagnostic criteria[2] for chronic inflammatory demyelinating polyneuropathy (CIDP). Patients 2 and 3 had electrodiagnostically mild polyneuropathies, with few to no abnormalities on needle examination. The EMG on patient 4 showed asymmetric denervation, compatible with a mononeuropathy multiplex. A polyradiculoneuropathy was present in patient 5, with prominent paraspinal muscle and distal limb muscle denervation. The findings in patients 1, 2, 3, and 5 were symmetric.

Sural nerve biopsies were performed on patients 2–5. Heterogeneity was clearly present, although most of the biopsies showed a mixed axonal and demyelinating picture. No widening of the myelin lamellae of the type seen in some IgM-associated neuropathies[21,29] was noted. Teased fiber data as well as the overall impression from both light and electron microscopy are provided in Table 4. While the biopsy of patient 4 did show perivascular mononuclear infiltrates around small epineurial blood vessels, a clear necrotizing vasculitis was not present. Immunofluorescence studies of patients 2, 3, and 4 revealed slight, diffuse

Table 3. Electrodiagnostic studies.

	Patient number					
	1	2	3	4	5	Normal
Ulnar motor						
Amp	8.6	ND	9.6	11.8	11.3	>6
DL	3.4	ND	2.7	4.1	3.2	<3.5
CV	31.2	ND	58.9	57.1	53	>49
F lat	43.6	ND	28.1	28.7	30.4	<31
P/D	0.53	ND	0.95	0.93	1.00	
Peroneal motor						
Amp	NR	4.3	2.4	NR	2.1	>2
DL	NR	6.4	4.9	NR	6.2	<6.1
CV	NR	38.3	37.5	NR	38.7	>41
F lat	NR	62.0	ND	NR	58.4	<55
P/D	NR	0.74	0.88	NR	0.90	
Ulnar sensory						
Amp	16.0	7.4	5.4	8.4	11.3	>10
DL	5.0	3.6	4.2	3.6	4.1	<3.5
CV	35.9	51.9	51.9	48.3	43.7	>53
Sural						
Amp	NR	6.9	NR	NR	NR	>6
DL	NR	4.4	NR	NR	NR	<4.2
CV	NR	38.9	NR	NR	NR	>40
Needle examination	Moderate symmetric distal denervation	Essentially normal	Mild symmetric distal denervation	Asymmetric denervation	Paraspinal and distal limb denervation	

Amp: amplitude (mV); DL: distal latency (ms); CV: conduction velocity (m/s); F lat: F-wave latency (ms); P/D: proximal/distal amplitude ratio; ND: not done; NR: no response.

Table 4. Sural nerve biopsy results.

Pt.	No. of fibers teased	Teased fiber classification (% of fibers)				Histological impression of neuropathy
		Myelin irregularity*	Segmental demyelination–remyelination	Axonal degeneration	Axonal regeneration	
2	72	7	14	4	3	Mixed, demyelinating > axonal
3	65	<2	9.5	0	20	Mixed, axonal > demyelinating
4	67	0	4	24	1.5	Axonal with minimal demyelination
5	80	12	8.75	3.75	2.5	Mixed, demyelinating ≥ axonal

*Focal myelin thickening at the node of Ranvier or the internode.

staining of the endoneurium and perineurium, interpreted as nonspecific since such staining was also seen in control nerves. There was no selective IgG, IgM, or IgA binding to the myelin sheath.

Three patients (patients 1, 3, and 4) were treated. Initial therapy in all consisted of prednisone 60 mg/d, which was gradually tapered. Patient 1 experienced a mild increase in strength with prednisone, then improved further with monthly intravenous gamma globulin infusions. After 1.5 years, she had only mild ankle dorsiflexor weakness (MRC grade 4+). Patient 3 had pain but no weakness at onset. Treatment resulted in a gradual resolution of the pain over the next 4 months, with an increase in functional capacity. Patient 4, whose main neurological deficit was distal lower extremity weakness, had some increased strength (by one MRC grade) in that muscle group over the first 2 months of treatment, but then died as a result of his underlying pulmonary disease. Of the untreated patients, patient 2 was lost to follow-up after his diagnostic evaluation, and patient 5 had only sensory symptoms, which were not felt to be sufficiently disabling to warrant the use of prednisone in light of his diabetes.

DISCUSSION

Patients with polyneuropathy and IgM or IgG monoclonal gammopathy are clinically, electrodiagnostically, and histologically heterogeneous,[9,10,15,16,19–22,25–29] presumably secondary to more than one mechanism of nerve fiber damage; some have primarily demyelinating neuropathies, while in others the neuropathy shows mainly axonal features. The best studied are those with IgM monoclonal gammopathy. Among these patients, those with elevated titers of antibodies to myelin-associated glycoprotein (MAG) are felt to form a relatively homogeneous group, presumably secondary to a uniform mechanism of nerve damage.[13,15,16,25,28]

Polyneuropathy occurs less commonly in association with IgA monoclonal gammopathy. Such patients constituted only 10 of 65 patients (15%) with polyneuropathy and MGUS in a recent Mayo Clinic review,[11] and only 5 of 50 cases (10%) seen at our institution with polyneuropathy and monoclonal or biclonal gammopathy of undetermined significance. This is roughly comparable with the 12% prevalence of IgA monoclonal gammopathies out of 7004 total patients with MGUS seen over a 27-year period at the Mayo Clinic.[11] Many of the cases of polyneuropathy and IgA MGUS described in the literature have had lambda light chains and osteosclerotic myeloma.[7,17] That subgroup is relatively homogeneous, typically resembling CIDP, with motor greater than sensory involvement, elevated cerebrospinal fluid protein levels, and electrodiagnostic studies showing slowed conduction velocities, increased distal latencies, and abnormal temporal dispersion/conduction block.

In contrast, patients with IgA monoclonal gammopathy and peripheral nervous system disease without osteosclerotic myeloma have been varied. Excluding those reported patients who appear to have motor neuron disease, those with malignant plasma cell dyscrasias, and those with osteosclerotic myeloma, there are 6 patients with polyneuropathy in whom the monoclonal gammopathy is of undetermined significance and who have been well described. Three are single cases,[3,4,14] while the other 3 constitute a small series of patients.[23] The clinical characteristics, primary mechanism of nerve damage, and immunological staining in these 6 patients and our 5 additional patients are summarized in Table 5.

As can be seen, 3 of the previously described

Table 5. Summary of patients with polyneuropathy and IgA monoclonal gammopathy of undetermined significance.

Reference	Light chain	Duration of symptoms	Main clinical feature*	Neuropathy type-studies†	Immunological studies‡
Nemni et al.,[23] case 1	Kappa	1y	S > M	Ax-edx	Polyclonal IgG staining of axons
Nemni et al.,[23] case 2	Kappa	1y	S only	Ax-edx	Polyclonal IgG staining of axons
Nemni et al.,[23] case 3	Lambda	2y	M >> S	Dem(?)-edx	Polyclonal IgG staining of axons
Baily et al.[3]	Kappa	20y	S, M, A	Dem-edx	IgA kappa staining of myelin sheath, endoneurium, perineurium
Hemachudha et al.[14]	Lambda	2 mo	M only	Dem-edx and bx	Not reported
Bosch et al.[4]	Lambda	14 mo	M > S	Ax-edx and bx	Diffuse IgG staining of endoneurium, subperineurial space
This report, case 1	Lambda	5 mo	M, S	Dem-edx	No bx
This report, case 2	Lambda	1y	S only	Mixed dem > ax-bx	Mild, diffuse IgM, IgG, and IgA staining of perineurium and endoneurium
This report, case 3	Kappa	8 mo	S only	Mixed ax > dem-bx	Mild, diffuse IgM, IgG, and IgA staining of perineurium and endoneurium
This report, case 4	Lambda	3y	M, S	Ax-edx and bx	Mild, diffuse IgM, IgG, and IgA staining of perineurium and endoneurium
This report, case 5	Lambda	2y	S only	Mixed dem ≥ ax-bx	Not done

**Main clinical feature of neuropathy: M = motor, S = sensory, A = autonomic.*
†Neuropathy type-studies: type of neuropathy and means of determination: ax = axonal, dem = demyelinating, edx = electrodiagnostic studies, bx = sural nerve biopsy.
‡Immunological studies = immunoperoxidase or immunofluorescence staining of sural nerve.

patients have had kappa light chains, while 3 have had lambda. Clinical presentations have varied greatly. Three have shown predominantly demyelinating features by electrodiagnostic studies or biopsy, while 3 appear to be primarily axonal. The clinical features and the primary mechanism of nerve damage did not correspond to the type of light chain present. None of the patients in whom immunological staining was performed showed IgA lambda or IgA kappa staining of a specific peripheral nerve component. Similarly, our 5 patients had both lambda and kappa light chains, and exhibited a variety of clinical, electrodiagnostic, and histological features. Thus, patients with polyneuropathy and IgA MGUS appear to be heterogeneous, similar to the more commonly seen patients with IgG and IgM MGUS. As with those patients, this most likely reflects a variety of mechanisms of nerve damage.

Only 2 of the patients described previously were treated. One,[14] who had serum antibodies to myelin-associated glycoprotein, improved dramatically with prednisone. The other[4] did not respond to plasma exchange, prednisone, or other immunosuppression. Patients with polyneuropathy and IgM or IgG MGUS have improved after treatment with a variety of immunosuppressive agents, including prednisone, chlorambucil, azathioprine, cyclophosphamide, plasma exchange, and intravenous gamma globulin.[5–7,9,12,14] In the absence of clear data favoring one specific therapeutic modality, we decided to treat initially with prednisone, and later used gamma globulin in 1 patient. Although our 3 treated patients all appeared to respond favorably, conclusions regarding treatment are limited in our small series; while 1 patient clearly improved with prednisone and gamma globulin, 1 patient's improvement was lim-

ited to the resolution of paresthesias, and another patient died 2 months into therapy after beginning to show some improved strength. The neuropathy was predominantly demyelinating in one of these patients and predominantly axonal in the other two. This is in agreement with previous reports that patients with either demyelinating or axonal polyneuropathies and IgM or IgG monoclonal gammopathies have responded favorably to treatment.[5,9,12,16,24,26,27] Because of the suggestion that immunomodulating therapy may be effective, the nature of the nerve injury should not exclude a trial of such therapy in these patients, at least until more definitive information on treatment is available.

We are unable to clarify the causal relationship, if any, between the monoclonal gammopathy and the polyneuropathy in these patients. This topic has been extensively discussed.[12,16,19,20,22,24,25,28,30,31] A causal relationship is considered likely in patients with IgM MGUS and antibodies to MAG, but has not been unequivocally proven. Several factors argue against a direct causal role for the IgA MGUS in our patients: (1) the comparable prevalence of IgA heavy chain in patients with MGUS with and without polyneuropathy; (2) the presence of a polyradiculoneuropathy in our diabetic patient (patient 5), which was indistinguishable from diabetic polyradiculoneuropathy; and (3) the lack of selective IgA binding to specific nerve components. Thus, the MGUS may be coincidental in our patients, or may simply be an indicator of an underlying autoimmune process. While the apparent response of some of our patients to immunomodulating therapy would support an autoimmune pathogenesis, the process presumably may be directed against a variety of peripheral nerve antigens, given the heterogeneity of clinical, electrodiagnostic, and histological presentations.

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