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Electrophysiological features and prognosis of peripheral neuropathy associated with IgM monoclonal gammopathy: a single-center analysis in South Korea

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Background: Clinical spectrum of immunoglobulin M (IgM) monoclonal gammopathy varies from IgM monoclonal gammopathy of unknown significance (IgM-MGUS) to hematological malignancies. We evaluated the clinical features, electrophysiological characteristics, and prognosis of patients with peripheral neuropathy associated with IgM monoclonal gammopathy (PN-IgM MG).
Methods: We retrospectively evaluated 25 patients with PN-IgM MG. Peripheral neuropathy was classified as axonal, demyelinating, or undetermined, based on electrophysiological studies. We classified the enrolled patients into the IgM-MGUS and malignancy groups, and compared the clinical and electrophysiological features between the groups.
Results: Fifteen patients had IgM-MGUS and 10 had hematologic malignancies (Waldenström's macroglobulinemia: two and B-cell non-Hodgkin's lymphoma: eight). In the electrophysiological evaluation, the nerve conduction study (NCS) criteria for demyelination were met in 86.7% of the IgM-MGUS group and 10.0% of the malignancy group. In particular, the distal latencies of the motor NCS in the IgM-MGUS group were significantly prolonged compared to those in the malignancy group (median, 9.1 ± 5.1 [IgM-MGUS], 4.2 ± 1.3 [malignancy], p = 0.003; ulnar, 5.4 ± 1.9 [IgM-MGUS], 2.9 ± 0.9 [malignancy], p = 0.001; fibular, 9.3 ± 5.1 [IgM-MGUS], 3.8 ± 0.3 [malignancy], p = 0.01; P-posterior tibial, 8.3 ± 5.4 [IgM-MGUS], 4.4 ± 1.0 [malignancy], p = 0.04). Overall treatment responses were significantly worse in the malignancy group than in the IgM-MGUS group (p = 0.004), and the modified Rankin Scale score at the last visit was higher in the malignancy group than in the IgM-MGUS group (2.0 ± 1.1 [IgM-MGUS], 4.2 ± 1.7 [malignancy], p = 0.001), although there was no significant difference at the initial assessment.
Conclusions: The risk of hematological malignancy should be carefully assessed in patients with PN-IgM MG without electrophysiological demyelination features.

Key words: Paraproteinemia; Monoclonal gammopathy of undetermined significance; Hematologic neoplasms; Peripheral nervous system diseases; Nerve conduction studies

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INTRODUCTION

The clinical spectrum of immunoglobulin M (IgM) monoclonal gammopathies varies from IgM monoclonal gammopathy of unknown significance (IgM-MGUS) (which does not present signs of malignancy or primary amyloidosis) to hematologic malignancies such as Waldenström's macroglobulinemia (WM) and B-cell non-Hodgkin's lymphoma (NHL).[1,2] IgM monoclonal gammopathies are frequently accompanied by peripheral neuropathy. Peripheral neuropathies associated with IgM monoclonal gammopathy (PN-IgM MG) are mostly sensory-predominant neuropathies with ataxic features, and motor deficits usually occur later in the course of the disease. Predominantly motor or purely motor neuropathies are rare.[3,4] Approximately one third of patients with IgM-MGUS (the most common monoclonal gammopathy) have peripheral neuropathy, and 5-10% prevalence of peripheral neuropathy has been reported in WM.[5] A previous study reported that 20.0% of patients with WM had prior diagnoses of peripheral neuropathy before WM disgnosis.[6] Therefore, early distinction of peripheral neuropathy related to hematologic malignancy from PN-IgM MG is important for timely and proper cancer management. Although PN-IgM MG has been studied extensively, research on the clinical and electrophysiological features and on the prognosis of PN-IgM MG is still lacking owing to the rarity of the disease. A previous study reported that evidence of demyelination in electrophysiological studies is more commonly observed in IgM-MGUS than in WM.[7] Another research reported that IgM-MGUS and peripheral neuropathy related to hematologic malignancy seem to have different treatment responses and prognoses, although their clinical manifestations are similar.[5] This study aimed to investigate the clinical features, electrophysiological characteristics, treatment response, and prognosis of patients with PN-IgM MG. In addition, we classified patients with PN-IgM MG into those with IgM-MGUS and those with malignancy, and compared the clinical and electrophysiological features between them.

MATERIALS AND METHODS

Subjects

We retrospectively collected data from 25 patients with peripheral neuropathy and serum immunofixation electrophoresis-confirmed IgM monoclonal gammopathy, aged ≥19 years between October 2005 and April 2021 in our center. Peripheral neuropathy was diagnosed based on the results of neurological examination and nerve conduction study (NCS), which were conducted during patient assessment. Patients with hereditary motor and sensory neuropathy or peripheral neuropathy related to other acquired etiologies such as diabetes mellitus, drug and heavy metal intoxication, vitamin deficiency, uremia, alcoholism, or systemic diseases were excluded. We classified patients with PN-IgM MG into the IgM-MGUS and malignancy groups based on the diagnosis of IgM monoclonal gammopathy. Patients with NHL or WM were classified into the malignancy group.

Clinical characteristics and laboratory findings

Demographic data, including age at onset, duration from onset to diagnosis, sex, and follow-up duration, were collected. In addition to demographic data, the Medical Research Council (MRC) sum score (Supplementary Material 1) and clinical manifestations, including sensory symptoms and signs, ataxia, and cranial nerve involvement, were evaluated based on neurological examination. The Neurological Disability Score (NDS) was evaluated at the first visit to assess the degree of neurological deficit associated with peripheral neuropathy (Supplementary Material 2). The NDS consists of items that assess motor, sensory, cranial nerve, and respiratory functions, and deep tendon reflexes. Previous studies have reported that the NDS is useful for the assessment of immune-mediated neuropathies, which frequently involve the cranial nerves, proximal muscles, and distal muscles.[8] Total NDS score ranges from 0 to 192, with a higher score indicating a worse degree of neuropathy. The results of complete blood count (CBC), initial serum IgM quantitation, titers of anti-myelin-associated ganglioside antibody (anti-MAG Ab), and levels of cerebrospinal fluid (CSF) protein (mg/dL, considered abnormal if >60.0 mg/dL) were recorded.

Electrophysiological studies and diagnosis of IgM monoclonal gammopathy

All patients had clinical symptoms of peripheral neuropathy and the presence of peripheral neuropathy was confirmed by electrophysiological studies. Peripheral neuropathy was classified as demyelinating, axonal, or undetermined during

the initial electrophysiological evaluation. Demyelinating and axonal patterns were defined based on the American Academy of Neurology's Ad Hoc Subcommittee criteria for chronic inflammatory demyelinating polyneuropathies.[9] Undetermined pattern was defined if the electrophysiological features were compatible with neither demyelinating nor axonal patterns. Distal motor latencies (DL), terminal latency index (TLI), compound muscle action potential (CMAP) amplitude, proximal to distal CMAP amplitude ratio, and motor conduction velocities (MCV) were evaluated in motor NCS of upper (median and ulnar nerves) and lower (fibular and posterior tibial nerves) extremities. Sensory nerve action potential (SNAP) amplitude and sensory conduction velocities (SCV) were evaluated in sensory NCS of upper (median and ulnar nerve) and lower (superficial fibular and sural nerve) extremities. The TLI was used to compare the conduction velocity of the distal segment (distal to the wrist) with that of the intermediate segment (wrist-to-elbow). The TLI was calculated using the formula developed by Shahani et al.;[10] distal conduction distance (mm)/forearm conduction velocity (m/s)/DL (ms). A TLI <0.25 was considered a predominantly demyelinating pattern. The presence of monoclonal proteins was determined by immunofixation following agarose gel electrophoresis. IgM-MGUS was defined as <10.0% plasma cells in the bone marrow and <3 g/dL of IgM monoclonal protein in the serum, and no evidence of end-organ damage. Hematological malignancies were diagnosed using bone marrow biopsy and ancillary tests, including skeletal X-radiography and body computed tomography. In our study, bone marrow study was performed in all patients.

Evaluation of treatment response and prognosis

Overall treatment response was classified as improved, stable, or worsened. Improvement or worsening of motor function was defined as an increase or decrease in the MRC sum score by at least >1 point.[11] Improvement or worsening of sensory function was defined as a decrease or an increase in the severity or extent of sensory symptoms, respectively, compared to the level prior to treatment. Overall treatment responses were defined as follows: 1) improved: one or more improvements in motor and sensory function; 2) stable: one of the motor and sensory functions was improved, and the other worsened or did not change; and 3) worsened: one or more worsening of motor and sensory functions. The modified Rankin Scale (mRS) scores at the initial and last visits were used to assess the prognosis (Supplementary Table 1).

Statistical analysis

The demographic and clinical features of the participants and the results of the electrophysiological evaluation were analyzed using descriptive statistics. Clinical features, electrophysiological characteristics, and treatment responses were compared between the IgM-MGUS and malignancy groups using the chi-squared test or Fisher's exact test. Clinical features, NCS parameters, and prognosis scales were compared using the Mann-Whitney *U*-test. Statistical analyses were performed using the IBM Statistical Package for the Social Sciences (software version 26, Armonk, NY, USA). Statistical significance was set at $p<0.05$.

Ethics statement

This study was approved by the Institutional Review Board of Severance Hospital (approval number: 4-2023-0413). All the procedures were performed in accordance with the principles of the Declaration of Helsinki. The requirement for informed consent was waived due to the retrospective nature of the study.

RESULTS

Demographic and clinical characteristics of study participants

Of the 25 patients (20 male and five female) included in this study, 15 (60.0%) had IgM-MGUS, eight (32.0%) had NHL, and two (8.0%) had WM. All participants were first diagnosed with peripheral neuropathy, followed by an additional diagnosis of IgM-MGUS or hematologic malignancies through evaluation for peripheral neuropathy. There were no transitions from IgM-MGUS to hematologic malignancies during the follow-up period of 20 months (median, 1-134 months). The demographic and clinical characteristics of the participants are presented in Table 1. The mean onset age of the patients with PN-IgM MG was 60.5 ± 11.3 years (range, 35-86 years) and the duration from onset to diagnosis of PN-IgM MG was 1.6 ± 2.3 years. The MRC sum score of the patients with PN-IgM MG was 68.4 ± 11.9 and the NDS score at first visit was 55.2 ± 35.0. Sensory symptoms, including hy-

Table 1. Demographic and clinical features of participants

	Total participants (n = 25)
Age (years)	60.5 ± 11.3
Duration from onset to diagnosis (years)	1.6 ± 2.3
Sex, male	20 (80.0)
Hematological diagnosis	
IgM-MGUS	15 (60.0)
NHL	8 (32.0)
WM	2 (8.0)
Symptoms	
Sensory symptoms	22 (88.0)
Limb weakness	15 (60.0)
Ataxia	11 (44.0)
Cranial nerve dysfunction	6 (24.0)
MRC sum score, initial	68.4 ± 11.9
NDS score, initial	55.2 ± 35.0
Median follow-up duration (months)	20 (1-134)
Results of complete blood count	
White blood cell count (10^3/μL)	7.7 ± 2.7
Hemoglobin (g/dL)	12.7 ± 2.4
Platelet count (10^3/μL)	263.8 ± 100.7
Initial serum IgM quantitation (mg/dL)	1,091.8 ± 1,067.1
Positive for anti-MAG Ab	8/16 (32.0)
Median titers of anti-MAG Ab (n = 8)	43,211 (2,792-14,6152)
Median level of CSF protein (mg/dL)	50.7 (27.8-448.0)
Overall treatment responses	
Improved	3 (12.0)
Stable	7 (28.0)
Worsened	11 (44.0)
Modified Rankin Scale (initial)	2.1 ± 1.0
Modified Rankin Scale (last)	2.9 ± 1.7
Modified Rankin Scale (initial) (≥ 3)	9 (36.0)
Modified Rankin Scale (last) (≥ 3)	12 (48.0)

Values are presented as mean ± standard deviation or number (%).
IgM-MGUS, IgM monoclonal gammopathy of unknown significance; NHL, B cell non-Hodgkin's lymphoma; WM, Waldenström's macroglobulinemia; MRC sum score, Medical Research Council sum score; NDS score, the neurological disability score; anti-MAG Ab, anti-myelin associated ganglioside antibody; CSF, cerebrospinal fluid.

Table 2. Details of result on electrophysiological evaluation

	Total participants (n = 25)
Electrophysiological classification	
Demyelinating	14 (56.0)
Axonal	5 (20.0)
Undetermined	6 (24.0)
Median nerve	
DL (ms)	7.1 ± 4.7[a]
TLI	0.32 ± 0.12
CMAP amplitude (mV)	9.4 ± 5.1
Proximal to distal CMAP amplitude ratio	76.9 ± 21.6
MCV (m/s)	39.2 ± 10.9[b]
SNAP amplitude (μV)	6.9 ± 6.3[b]
SCV (m/s)	35.9 ± 8.0[b]
Ulnar nerve	
DL (ms)	4.4 ± 2.0[a]
TLI (considered abnormal, if <0.25)	0.52 ± 0.31
CMAP amplitude (mV)	9.9 ± 5.2
Proximal to distal CMAP amplitude ratio	73.4 ± 21.2
MCV (m/s)	42.0 ± 12.7[b]
SNAP amplitude (μV)	6.2 ± 4.9[b]
SCV (m/s)	36.3 ± 8.1[b]
Fibular nerve	
DL (ms)	6.9 ± 4.6[a]
TLI (considered abnormal, if <0.25)	0.47 ± 0.20
CMAP amplitude (mV)	2.8 ± 2.9
MCV (m/s)	34.6 ± 11.3[b]
Superficial fibular nerve	
SNAP amplitude (μV)	5.4 ± 4.3
SCV (m/s)	32.1 ± 4.8
Posterior tibial nerve	
DL (ms)	6.4 ± 4.4[a]
TLI (considered abnormal, if <0.25)	0.46 ± 0.17
CMAP amplitude (mV)	7.2 ± 6.4
MCV (m/s)	35.9 ± 11.0[b]
Sural nerve	
SNAP amplitude (μV)	7.6 ± 8.9
SCV (m/s)	32.0 ± 6.9[b]

Values are presented as mean ± standard deviation or number (%).
DL, distal motor latencies; TLI, terminal latency index; CMAP amplitude, compound muscle action potential amplitude; MCV, motor conduction velocities; SNAP amplitude, sensory nerve action potential amplitude; SCV, sensory conduction velocities.
[a]Indicate the result is above the upper limit of normal.
[b]Indicate the result is below the lower limit of normal.

Table 3. Comparison of clinical and electrophysiological characteristics between the IgM-MGUS and malignancy group

	IgM-MGUS (n = 15)	Malignancy (n = 10)	*p*
Age (years)	62.2 ± 12.8	58.0 ± 8.8	0.38
Duration from onset to diagnosis (years)	2.5 ± 2.7	0.3 ± 0.5	0.01[a]
MRC sum score, total 80	72.8 ± 8.2	61.9 ± 14.0	0.02[a]
NDS score	45.4 ± 24.3	70.5 ± 45.2	0.21
Follow-up duration (months)	25.6 ± 31.4	41.3 ± 41.4	0.29
White blood cell count (10^3/μL)	9.1 ± 2.2	5.6 ± 1.8	<0.001[a]
Hemoglobin (g/dL)	13.9 ± 1.8	10.9 ± 2.1	0.001[a]
Platelet count (10^3/μL)	302.3 ± 105.0	206.0 ± 60.8	0.02[a]
Initial serum IgM quantitation (mg/dL)	891.8 ± 646.9	1,371.8 ± 1,468.4	0.35
Positive for anti-MAG Ab	7/10 (46.7)	1/6 (10.0)	0.12
The titers of anti-MAG Ab (n = 8)	69,559.2 ± 52,586.3	18,226.0	[b]
The level of CSF protein (mg/dL)	74.1 ± 53.0	135.3 ± 159.0	0.55
Electrophysiological classification			0.000[a]
Demyelinating	13 (86.7)	1 (10.0)	
Non-demyelinating	2 (13.3)	9 (90.0)	
Median nerve			
DL (ms)	9.1 ± 5.1	4.2 ± 1.3	0.003[a]
TLI (considered abnormal, if <0.25)	0.26 ± 0.08	0.41 ± 0.10	<0.001[a]
CMAP amplitude (mV)	9.7 ± 5.1	8.9 ± 5.4	0.69
MCV (m/s)	35.0 ± 10.8	45.5 ± 7.9	0.02[a]
Ulnar nerve			
DL (ms)	5.4 ± 1.9	2.9 ± 0.9	0.001[a]
TLI (considered abnormal, if <0.25)	0.38 ± 0.09	0.73 ± 0.40	0.02[a]
CMAP amplitude (mV)	10.5 ± 5.1	9.1 ± 5.4	0.52
MCV (m/s)	35.9 ± 11.3	51.1 ± 9.0	0.002[a]
Fibular nerve			
DL (ms)	9.3 ± 5.1	3.8 ± 0.3	0.01[a]
TLI (considered abnormal, if <0.25)	0.38 ± 0.15	0.58 ± 0.21	0.02[a]
CMAP amplitude (mV)	2.8 ± 2.5	2.8 ± 3.6	0.97
MCV (m/s)	31.1 ± 12.0	38.9 ± 9.1	0.13
Posterior tibial nerve			
DL (ms)	8.3 ± 5.4	4.4 ± 1.0	0.04[a]
TLI (considered abnormal, if <0.25)	0.40 ± 0.11	0.53 ± 0.20	0.07
CMAP amplitude (mV)	6.1 ± 5.1	8.5 ± 7.7	0.41
MCV (m/s)	32.7 ± 10.6	39.4 ± 10.9	0.17
Overall treatment responses			0.004[a]
Improved	3 (20.0)	0 (0.0)	
Stable	6 (40.0)	1 (10.0)	
Worsened	2 (13.3)	9 (90.0)	
Modified Rankin Scale (initial)	2.0 ± 1.1	2.3 ± 0.8	0.46
Modified Rankin Scale (last)	2.0 ± 1.1	4.2 ± 1.7	0.001[a]

Values are presented as mean ± standard deviation or number (%).

IgM-MGUS, IgM monoclonal gammopathy of unknown significance; MRC sum score, Medical Research Council sum score; NDS score, The neurological disability score; anti-MAG Ab, anti-myelin associated ganglioside antibody; CSF, cerebrospinal fluid; DL, distal motor latencies; TLI, terminal latency index; CMAP amplitude, compound muscle action potential amplitude; MCV, motor conduction velocities.

[a]Indicates that the results are statistically significant ($p<0.05$).

[b]Indicate that analysis could not available due to lack of valid cases.

poesthesia, paresthesia, and pain, were the most common symptoms (88.0%), followed by limb weakness (60.0%), ataxia (44.0%), and cranial nerve dysfunction (24.0%). The mean initial serum IgM quantitation of the patients was 1,091.8 ± 1,067.1 (mg/dL, considered abnormal if ≥230 mg/dL). Eight patients (32.0%) tested positive for anti-MAG Ab. Of the eight patients, seven had IgM-MGUS and the other had NHL. The median level of CSF protein was 50.9 (ranged from 27.8 to 448.0, mg/dL). In terms of overall treatment responses, three patients (12.0%) improved, seven patients (28.0%) were stable, and 11 patients (44.0%) worsened despite treatment. Of the four patients whose treatment response could not be evaluated, three were diagnosed with IgM-MGUS and no immune-modulating treatment was administered. The other patient was diagnosed with IgM-MGUS and had only 1 month of follow-up; therefore, the treatment response could not be accurately evaluated. The mean mRS score changed from 2.1 ± 1.0 at initial visit to 2.9 ± 1.7 at the last visit. Patients with 3 or more mRS score were nine patients (36.0%) in the initial assessment, and 12 (48.0%) in the last assessment.

Electrophysiological characteristics of study participants

The results of the electrophysiological evaluations are shown in Table 2. In the electrophysiological studies, 14 patients (56.0%) had a demyelinating pattern, five (20.0%) had an axonal pattern, and six (24.0%) had undetermined patterns of peripheral neuropathies. The mean DL of median, ulnar, fibular, and posterior tibial motor nerves were increased above the upper limit of normal (ms, 7.1 ± 4.7 [median, normal range 2.2-3.9]; 4.4 ± 2.0 [ulnar, normal range 1.6-3.0]; 6.9 ± 4.6 [fibular, normal range 2.2-5.3]; 6.4 ± 4.4 [posterior tibial, normal range 2.5-5.4], respectively), and mean MCV of these nerves were decreased below the lower limit of normal (m/s, 39.2 ± 10.9 [median, normal range 50.5-68.1]; 42.0 ± 12.7 [ulnar, normal range 51.1-70.1]; 34.6 ± 11.3 [fibular, normal range 40.5-57.5]; 35.9 ± 11.0 [posterior tibial, normal range 41.1-58.6]). In sensory NCS, mean SNAP amplitude of median and ulnar sensory nerves, and mean SCV of median, ulnar, and sural nerves were slightly decreased below the lower limit of normal.

Comparison of clinical and electrophysiological characteristics between the IgM-MGUS group and malignancy group

The clinical and electrophysiological features were compared between the IgM-MGUS and malignancy groups (Table 3). Duration from onset to diagnosis was shorter, and MRC sum score and CBC count were lower in the malignancy group than in the IgM-MGUS group (duration from onset to diagnosis [years], IgM-MGUS [2.5 ± 2.7], malignancy [0.3 ± 0.5], $p = 0.01$; MRC sum score, IgM-MGUS [72.8 ± 8.2], malignancy [61.9 ± 14.0], $p = 0.02$; CBC count (white blood cell [10^3/μL], IgM-MGUS [9.1 ± 2.2], malignancy [5.6 ± 1.8], $p<0.001$; hemoglobin [g/dL], IgM-MGUS [13.9 ± 1.8], malignancy [10.9 ± 2.1], $p = 0.001$; platelet [10^3/μL], IgM-MGUS [302.3 ± 105.0], malignancy [206.0 ± 60.8], $p = 0.02$). In electrophysiological examination, 86.7% of IgM-MGUS and 10.0% of malignancy group showed demyelinating pattern ($p<0.001$). Significant differences were observed in distal latencies of motor NCS (median [ms], IgM-MGUS [9.1 ± 5.1], malignancy [4.2 ± 1.3], $p = 0.003$; ulnar, IgM-MGUS [5.4 ± 1.9], malignancy [2.9 ± 0.9], $p = 0.001$; fibular, IgM-MGUS [9.3 ± 5.1], malignancy [3.8 ± 0.3], $p = 0.01$; posterior tibial, IgM-MGUS [8.3 ± 5.4], malignancy [4.4 ± 1.0], $p = 0.04$), and in TLI of median, ulnar, and fibular nerve (median, IgM-MGUS [0.26 ± 0.08], malignancy [0.41 ± 0.10], $p<0.001$; ulnar, IgM-MGUS [0.38 ± 0.09], malignancy [0.73 ± 0.40], $p = 0.02$; fibular, IgM-MGUS [0.38 ± 0.15], malignancy [0.58 ± 0.21], $p = 0.02$) between the two groups. There were no significant differences in sensory NCS parameters. Overall, treatment responses were significantly worse in the malignancy group than in the IgM-MGUS group ($p = 0.004$). The mRS performed at last visit was significantly higher in the malignancy group than in the IgM-MGUS group (IgM-MGUS 2.0 ± 1.1, malignancy 4.2 ± 1.7, $p = 0.001$), although there was no significant difference in initial mRS between the groups.

DISCUSSION

Paraproteinemia is a heterogeneous group of disorders resulting from monoclonal protein production and deposition, which occurs in plasma cell disorders such as IgM-MGUS, WM, multiple myeloma, amyloidosis, polyneuropathy, organomegaly, endocrinopathy, M-protein, skin changes

syndrome, cryoglobulinemia, and other lymphoproliferative disorders.[5,12] The strongest association between paraproteinemia and peripheral neuropathy is found in IgM paraprotein. Approximately 50.0% of patients with IgM monoclonal gammopathies have symptomatic neuropathy. Immunohistochemistry shows direct binding of the IgM monoclonal protein and light chains to peripheral myelin nerve sheaths in patients with PN-IgM MG.[12]

Early distinction of peripheral neuropathy related to hematologic malignancy from PN-IgM MG is important for timely and proper management of cancer and peripheral neuropathy. In our study, evidence of demyelination in NCS was more commonly observed in the IgM-MGUS group than in the malignancy group, and significant differences were observed in the distal latencies of motor NCS between the two groups. In addition, most patients in the malignancy group showed axonal neuropathy in the NCS. We hypothesized that peripheral neuropathy in hematologic malignancies might be due to deposition of circulating IgM monoclonal protein in peripheral nerve axon and its surrounding structures, and although extremely rare, direct neoplastic cell infiltration could lead to axonal injury.[6] Similar to the results of our study, a previous study reported that 73.0% of bone marrow biopsy confirmed that WM patients had only primary axonal features on NCS whereas 62.0% of IgM-MGUS patients had demyelinating features.[7] Other previous research on peripheral neuropathy of WM suggested that peripheral neuropathies in WM may be related to specific antigenic targets of the monoclonal serum IgM, including MAG and sulfatide, or unidentified antigens on peripheral nerves. In previous a study, demyelination was found in only 8.0% of WM neuropathy, and IgM M-proteins in patients with WM bound to sulfatide (5.0%) and MAG (4.0%) less often than the expected frequency of 28.0% to 62.0%.[6] Immunoglobulin M binding to MAG probably plays a pathogenic role in the production of demyelinating neuropathies. Although evaluation of specific targeting antibodies could not be performed except for anti-MAG Ab in our study, the proportion of positivity for anti-MAG Ab was 46.7% in the IgM-MGUS group and 10.0% in the malignancy group. A lower frequency of anti-MAG Ab occurred in the malignancy group (without statistical significance) in our study ($p = 0.12$).

IgM-MGUS is a premalignant condition that may develop into a lymphoid malignancy such as WM and indolent B-cell lymphoma. The risk of transformation to lymphoid malignancy in IgM-MGUS is approximately 2-3% per year. IgM-MGUS is defined as <10.0% plasma cells in the bone marrow and <3 g/dL of IgM monoclonal protein in the serum, and no evidence of end-organ damage.[13] IgM-MGUS and peripheral neuropathy related to hematologic malignancy seem to have different treatment response and prognosis, although their clinical manifestations are similar.[5] For hematologic malignancies, treating the underlying disease takes priority and may control the peripheral neuropathy. In contrast, treatment for IgM-MGUS is not required in asymptomatic cases; however, treatment may be required to lower the monoclonal paraprotein levels in symptomatic cases. Approximately 25-30% of patients with PN-IgM MG have moderate disability at 10 years.[4,14] In our study, the mean mRS score performed at the last visit was approximately 3, which indicates moderate disability that requires some help but is able to walk without assistance. Moreover, the mRS score at the last visit was higher in the malignancy group than in the IgM-MGUS group, although there was no significant difference between the two groups at the initial assessment. Therefore, it is important to routinely monitor whether IgM-MGUS switches to malignancy because the treatment and prognosis are quite different.

This retrospective study had several limitations. First, the number of subjects in our study was relatively small and the study was performed at a single tertiary center. IgM-MGUS is uncommon in Asian populations. A previous study in Nagasaki, Japan reported an overall prevalence of 2.1% for MGUS, and these data yielded an estimated prevalence of 0.16% for IgM-MGUS in this population. Also, a survey of 1,600 Chinese patients undergoing electrophoresis for suspected monoclonal gammopathy in Hong Kong found that 0.56% of MGUS was due to IgM monoclonal protein.[15] Further multicenter and multi-national studies with a large sample size are required. Second, we could not perform nerve biopsy in all the enrolled patients. Sural nerve biopsy was performed in only two patients diagnosed with NHL. Nerve biopsy revealed a pattern of axonal neuropathy, and malignant cells were not observed in all patients. If nerve biopsies were performed in more patients, the electrophysiological differences in PN-IgM MG could be clearer. Third, we used the mRS at the initial and final visits as a scale for prognosis assessment in this study. The mRS mostly reflects

the degree of disability and dependence on the daily activities of patients with many neurological diseases. Its reliability has been established in patients with stroke; however, although it has been widely used in many previous studies, no formal clinometric evaluation of the mRS has been performed in patients with peripheral neuropathy. The mRS has the disadvantage of relatively insufficient reflection of upper-limb dysfunction. Therefore, in addition to the mRS, detailed scales that reflect the functions of the upper and lower extremities, such as the Overall Disability Sum Score or the Neuropathy Disability Scale, are needed for prognosis assessment. Furthermore, the prognosis in the malignancy group may be affected by various other situations caused by complications accompanying cancer, the effect of chemotherapy, and the deterioration of general conditions. The mRS score could not accurately reflect the treatment response or prognosis for peripheral neuropathy because some patients did not undergo serial NCS tests in this study. In addition, no patients were converted from IgM-MGUS to hematologic malignancy during the follow-up period in this study, but if the follow-up period was longer, there could have been patients with malignant transformation and their clinical data and serial NCS tests could be analyzed. Further studies are required to reflect this.

In conclusion, 40.0% of patients with PN-IgM MG had hematologic malignancy and only 10.0% of patients with malignancy showed demyelinating neuropathy, whereas more than 85.0% of patients with IgM-MGUS had demyelinating neuropathy. This suggests that the risk of hematological malignancy should be carefully assessed in patients with PN-IgM MG without electrophysiological demyelination. Early detection and appropriate management of hematologic malignancies in patients with PN-IgM MG will improve the prognosis and survival.

Conflicts of Interest

The authors declare no conflicts of interest.

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REFERENCES

1. Kyle RA, Garton JP. The spectrum of IgM monoclonal gammopathy in 430 cases. Mayo Clin Proc 1987;62:719-731.
2. Cao XX, Meng Q, Mao YY, Su W, Zhen JF, Shen KN, et al. The clinical spectrum of IgM monoclonal gammopathy: a single center retrospective study of 377 patients. Leuk Res 2016;46:85-88.
3. Chassande B, Léger JM, Younes-Chennoufi AB, Bengoufa D, Maisonobe T, Bouche P, et al. Peripheral neuropathy associated with IgM monoclonal gammopathy: correlations between M-protein antibody activity and clinical/electrophysiological features in 40 cases. Muscle Nerve 1998;21:55-62.
4. Chaudhry HM, Mauermann ML, Rajkumar SV. Monoclonal gammopathy-associated peripheral neuropathy: diagnosis and management. Mayo Clin Proc 2017;92:838-850.
5. Ramchandren S, Lewis RA. Monoclonal gammopathy and neuropathy. Curr Opin Neurol 2009;22:480-485.
6. Levine T, Pestronk A, Florence J, Al-Lozi MT, Lopate G, Miller T, et al. Peripheral neuropathies in Waldenström's macroglobulinaemia. J Neurol Neurosurg Psychiatry 2006;77:224-228.
7. Klein CJ, Moon JS, Mauermann ML, Zeldenrust SR, Wu Y, Dispenzieri A, et al. The neuropathies of Waldenström's macroglobulinemia (WM) and IgM-MGUS. Can J Neurol Sci 2011;38:289-295.
8. Kim JE, Bae JS. Clinical scales for peripheral neuropathy-revision 2021. J Korean Neurol Assoc 2021;39:2-14.
9. Research criteria for diagnosis of chronic inflammatory demyelinating polyneuropathy (CIDP). Report from an Ad Hoc Subcommittee of the American Academy of Neurology AIDS Task Force. Neurology 1991;41:617-618.
10. Shahani BT, Young RR, Potts F, Maccabee P. Terminal latency index (TLI) and late response studies in motor neuron disease (MND), peripheral neuropathies and entrapment syndromes. Acta Neurol Scand 1979;60:118.
11. Delmont E, Azulay JP, Giorgi R, Attarian S, Verschueren A, Uzenot D, et al. Multifocal motor neuropathy with and without conduction block: a single entity? Neurology 2006;67:592-596.
12. Silberman J, Lonial S. Review of peripheral neuropathy in plasma cell disorders. Hematol Oncol 2008;26:55-65.
13. Jalali S, Shi J, Ahsan N, Wellik L, Serres M, Buko A, et al. Progression from monoclonal gammopathy of undetermined significance of the immunoglobulin M class (IgM-MGUS) to Waldenstrom Macroglobulinemia is associated with an alteration in lipid metabolism. Redox Biol 2021;41:101927.
14. Niermeijer JM, Fischer K, Eurelings M, Franssen H, Wokke JH,

Notermans NC. Prognosis of polyneuropathy due to IgM monoclonal gammopathy: a prospective cohort study. Neurology 2010;74:406-412.

15. McMaster ML, Landgren O. Prevalence, clinical aspects, and natural history of IgM MGUS. Cytometry B Clin Cytom 2010; 78:S91-S97.