Malignant transformation in polyneuropathy associated with monoclonal gammopathy

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Abstract—*Objective:* To assess the frequency of hematologic malignancies at diagnosis and to determine the incidence and predictors of malignant transformation during follow-up in patients with polyneuropathy associated with monoclonal gammopathy. *Methods:* Potential predictors of malignant transformation from medical history, hematologic, neurologic, and laboratory examination performed each 6 months were evaluated by univariable and multivariable Cox proportional hazard analysis. *Results:* Of 193 patients with polyneuropathy associated with monoclonal gammopathy, 17 patients had a hematologic malignancy at diagnosis. The incidence rate of malignant transformation in 176 patients without a malignancy at diagnosis was 2.7/100 patient years. Weight loss, progression of the polyneuropathy, unexplained fever or night sweats, and M-protein level were independent predictors. *Conclusions:* Since hematologic malignancies occur frequently in polyneuropathy associated with monoclonal gammopathy, the authors suggest that all patients should be screened at diagnosis and subsequently during follow-up if malignant transformation is suspected.

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Monoclonal gammopathy of undetermined significance (MGUS) occurs in 0.1 to 3% of the normal population and prevalence rises with age.[1] MGUS is characterized by the presence of a monoclonal protein (M-protein) in serum or urine without an underlying hematologic malignancy. Criteria for MGUS include a serum M-protein level less than 30 g/L, a bone marrow plasma cell infiltration of less than 10%, and absence of lytic bone lesions, anemia, hypercalcemia, or renal insufficiency, and stability of the M-protein level.[2,3] Persons with MGUS are asymptomatic and have no signs of hematologic malignancies, including fatigue, weight loss, bone pain, or susceptibility to infections. However, 1% of patients with MGUS develop a hematologic malignancy per year, and the risk of malignant transformation persists even after 30 years of follow-up.[4] In IgG MGUS malignant transformation to a plasma cell malignancy has been reported to be 1% per year,[5] and in IgM MGUS malignant transformation to a malignant lymphoid disorder like lymphoma or immunocytoma occurs in 1.5% of patients per year.[6]

The relation between polyneuropathy and MGUS is supported by epidemiologic, pathologic, and passive transfer studies.[7-11] In a retrospective cohort analysis we found that 22% of patients with polyneuropathy associated with MGUS developed a hematologic malignancy during long-term follow-up of median 6 years.[12] This suggests a higher frequency of hematologic malignancies in MGUS associated with polyneuropathy than in MGUS without polyneuropathy.

Therefore, we prospectively studied 193 nonselected patients with polyneuropathy associated with monoclonal gammopathy with a mean follow-up duration of 3 years, and assessed the frequency of underlying hematologic malignancies at diagnosis and the incidence of malignant transformation during follow-up. In addition, we analyzed which factors predicted malignant transformation in 104 patients without a hematologic malignancy at diagnosis in whom bone marrow examination was performed at the beginning and the end of follow-up.

Methods. *Patients.* From January 1995 to August 2004, 193 patients with polyneuropathy associated with MGUS were identified at the Department of Neuromuscular Diseases of the University Medical Center Utrecht. These patients were referred to our clinic from all over the country for diagnosis and screening for causes. Before inclusion none of the patients was treated with chemotherapeutics. All patients with polyneuropathy and M-protein without other causes of the neuropathy were included after signed informed consent.[13] In all patients the initial workup included 1) medical history, 2) neurologic examination, 3) routine laboratory analysis, 4) electrophysiologic studies, including nerve conduction and concentric needle examination using standardized techniques, identifying a predominantly axonal or demyelinating neuropathy according to the criteria of the American Academy of Neurology (AAN),[14,15] 5) a survey for M-protein by immunofixation of serum and 10 x concentrated urine, 6) antibody reactivity,[16,17] 7) physical examination by a hematologist, 8) skeletal X-ray, 9) X-ray of the lungs, 10) sonography or CT scan of the abdomen (on indication), and 11) bone marrow investigation. Bone marrow as-

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pirates and biopsies were obtained from the crista iliaca posterior and viewed by a pathologist. Additional investigations included immunophenotyping with specific plasma cell, B cell, and T cell monoclonal antibodies. Congo red staining was performed for the detection of amyloidal deposits. In patients suspected of amyloidosis, i.e., painful axonal neuropathy or autonomic function disorder, without amyloidal deposits in bone marrow, Congo red staining of a rectal biopsy or a sural nerve biopsy was performed. During follow-up patients were examined each 6 months, including 1) medical history, 2) physical examination, 3) neurologic examination, 4) routine laboratory analysis, and 5) determination of the level of M-protein. Duration of follow-up was defined by the time between the first hematologic screening and the diagnosis of an endpoint or the end of the study. We obtained the following variables: fatigue, defined by difficulty in performing normal daily activities; unexplained bone pain, defined as consistent localized pain other than joint or muscle pain; infections; B-symptoms, defined by unexplained fever, night sweats, unexplained weight loss (>5 kg/6 months); progression of the polyneuropathy, defined by deterioration of the neuropathy leading to disability (graded with decrease of the Rankin disability score of one point) or decrease of sensory function or strength of one point in 6 months.[18,19] Strength was measured with MRC grading system in six muscles of both arms (deltoid, biceps and triceps brachii, finger extensors, finger flexors, and first interosseus) and both legs (iliopsoas, quadriceps femoris, hamstrings, anterior tibial, gastrocnemius, and peroneal) leading to a maximum score of 120. Sensory functions, both touch and pinprick sense, were graded as normal = 4, abnormal distal to wrist/ankle = 3, distal half forearm/leg = 2, distal to elbow/knee = 1, distal to axilla/groin = 0. Vibration sense studied with tuning fork perception (128 Hz) was graded as present on middle finger/hallux = 4, ulnar styloid/medial malleolus = 3, elbow/knee = 2, clavicula/crista iliaca = 1, no perception = 0. Joint position sense was graded as present of middle finger/hallux = 2, diminished = 1, absent = 0. Summation of all sensory modalities could lead to a maximum score of 56. We obtained the following laboratory variables: M-protein isotype; M-protein level (g/L), significant rise of M-protein level (>25% if M-protein level $\geq$ 5 g/L with an absolute rise of > 5 g/L, minimal 5 g/L if M-protein level < 5 g/L),[20] measured at least at two different time points; and anemia (hemoglobin level < 7.4 mmol/L $\leq$ 12 g/L in women and < 8.6 mmol/L $\leq$ 14 g/L in men).

Outcome. The main outcome of the study was malignant transformation to a hematologic malignancy, i.e., multiple myeloma, plasmacytoma, amyloidosis, immunocytoma, Non-Hodgkin's lymphoma, Castleman's disease, and POEMS (polyneuropathy, organomegaly, endocrinopathy, M-protein, and skin symptoms). Criteria for multiple myeloma and plasmacytoma were defined according to Kyle and Greipp[21] and multiple myeloma patients were classified according to Salmon and Durie.[22] Indolent myeloma and smoldering myeloma fulfilling the criteria of Stage I myeloma were classified as Stage 1 myeloma. Immunocytoma was defined based on WHO criteria, i.e., infiltration of the bone marrow of > 25% by mature B-cells. Non-Hodgkin lymphoma was defined according to the REAL classification.[23] MGUS was defined according to Kyle.[2]

Statistical analysis. The incidence of malignant transformation during follow-up was assessed in all patients without a hematologic malignancy at diagnosis. The analyses of predictors for malignant transformation during follow-up were performed on patients without a hematologic malignancy at the initial hematologic screening at baseline (at diagnosis), with complete data on important predictive factors and bone marrow examination at the beginning and the end of follow-up. The association between each predictor and malignant transformation was first assessed by univariable Cox proportional hazards analysis, with the hazard ratio (HR) and 95% CI as measures of association.

Variables that were univariately associated with hematologic malignancies at follow-up ($p < 0.1$) were then included in a multivariable Cox proportional hazards analyses model to evaluate their independent contribution in the prediction of malignancies. First we included variables that can be obtained by history taking and physical examination, thereafter we included laboratory variables. Model reduction was performed by excluding variables that were not significantly related to hematologic malignancies (HR with $p < 0.05$) from the overall model by the step-down method. The relationship between malignancy (at baseline or at follow-up) and mortality was studied using a statistical model relating a determinant whose status changes over time to survival type (censored) outcome data, i.e., Cox regression with time-varying covariates.[24] The results were expressed as HR (and 95% CI). The relationship between survival and type of monoclonal gammopathy was analyzed using Kaplan-Meier survival analysis.

Table 1 *Clinical characteristics of 193 patients with polyneuropathy associated with monoclonal gammopathy in percentage unless otherwise specified*

	At diagnosis		During follow-up	
	MGUS, n = 176	Malignancy, n = 17	MGUS, n = 159	Malignancy, n = 17
Age at onset, mean (SD), y	60 (10)	57 (10)	60 (10)	56 (10)
Follow-up, mean (SD), mo			38 (32)	55 (39)
Sex, male	68	75	69	61
Fatigue	21	50*	18	44*
Bone pain	6	13	5	17
Infections	1	6	1	6
Night sweats/unexplained fever	2	13	1	11*
Weight loss	10	44†	8	24*
Kidney dysfunction	3	6	3	11
Progression of polyneuropathy			44	89‡
Autonomic function disorder	7	17	7	0

* = $p < 0.05$.
† = $p < 0.01$.
‡ = $p < 0.001$.

MGUS = monoclonal gammopathy of undetermined significance; malignancy = hematologic malignancy; kidney dysfunction = serum creatinine level > 20 mg/L.

Results. *Baseline and neurologic characteristics.* For this study 193 patients underwent neurologic and hematologic screening. Most patients were men (69%) with a mean age of 60 years (table 1). Thirty-four patients had monoclonal IgM anti-MAG antibodies (29% of the patients with IgM monoclonal gammopathy or IgM/IgG biclonal gammopathy, table 2). Twenty-three patients had a slowly progressive demyelinating polyneuropathy associated with monoclonal IgM anti-MAG antibodies with ataxia or sensorimotor symptoms and signs. Eleven patients with anti-MAG antibodies had a more progressive disease course. Of the 83 patients with IgM monoclonal gammopathy (or biclonal gammopathy with IgM) without anti-MAG antibody reactivity 64% had a demyelinating polyneuropathy with predominance of sensory symptoms and signs. Of the 66 patients with IgG monoclonal gammopathy 73% had axonal polyneuropathy with predominance of sensory symptoms and signs. Nine patients had IgA monoclonal gammopathy with axonal sensory polyneuropathy.

Frequency of underlying hematologic malignancies. Of the 193 patients, 17 (9%) had a hematologic malignancy at first screening (3 multiple myeloma [2 stage I and 1 stage III multiple myeloma], 3 plasmacytoma, 2 amyloidosis, 4 immunocytoma, 1 non-Hodgkin's lymphoma and multiple myeloma, 1 Castleman's disease, 3 POEMS). Characteristics of patients are summarized in tables 1 and 2.

Incidence of malignant transformation during follow-up. The incidence of malignant transformation during follow-up was assessed in 176 patients with polyneuropathy associated with MGUS in whom no hematologic malignancy was found after extensive hematologic screening at baseline. Bone marrow examination was performed in 139 patients (79%). After a mean follow-up of 3 years, 17 patients (incidence rate 2.7 per 100 person-years) developed a hematologic malignancy (4 multiple myeloma [3 stage I and 1 stage III multiple myeloma], 1 plasmacytoma, 10 immunocytoma, 1 Non-Hodgkin's lymphoma, and 1 POEMS). Five patients with polyneuropathy associated with IgM anti-MAG antibodies and a progressive disease course had malignant transformation (4 immunocytoma, 1 Non-Hodgkin's lymphoma).

Predictive factors for malignant transformation. The analyses of predictive factors for malignant transformation during follow-up were restricted to 104 patients without a hematologic malignancy at diagnosis and complete data on important predictors including bone marrow examination at the beginning and end of follow-up (88 with MGUS and 16 with a hematologic malignancy at the end of follow-up). Of the 104 patients included in the analyses of potential predictors more patients had a progressive polyneuropathy and a hematologic malignancy than in the 72 patients who were not included in these analyses. Of these 72 patients 45 patients were lost to follow-up. Other characteristics did not differ. The HRs for the associations between the potential predictors and hematologic malignancy determined with univariable analysis are presented in table 3. In multivariable analysis unexplained weight loss, progression of the polyneuropathy, unexplained fever or night

Table 2 *Laboratory characteristics of 193 patients with polyneuropathy associated with monoclonal gammopathy in percentage unless otherwise specified*

	At diagnosis		During follow-up	
	MGUS, n = 176	Malignancy, n = 17	MGUS, n = 159	Malignancy, n = 17
IgM	56	13	55	61
IgG	30	53	32	17
IgA	4	13	3	17
Biclonal gammopathy	10	20	11	6
Kappa	63	38	63	61
Lambda	28	38	27	39
Kappa and Lambda	10	25	11	0
Monoclonal protein level, mean (SD), g/L	3 (6)	7 (9)*	3 (5)	10 (9)†
Increasing monoclonal protein level			6	41†
Anemia	22	50	20	50
Demyelinating EMG	56	69	54	72
Monoclonal population in bone marrow	48	64	39	100†
Plasma cell, mean (SD), %	3 (3)	3 (4)	2 (3)	6 (7)
B cell, mean (SD), %	8 (6)	9 (8)	7 (4)	15 (8)*

* $p < 0.05$.
† $p < 0.001$.

MGUS = monoclonal gammopathy of undetermined significance; malignancy = hematologic malignancy; IgM, IgG, IgA = IgM, IgG, IgA monoclonal gammopathy; kappa, lambda = kappa, lambda light chain; kappa and lambda = biclonal gammopathy with kappa and lambda; anemia = hemoglobin level < 12 g/L (<7.4 mmol/L) in women, < 14 g/L (<8.6 mmol/L) in men; demyelinating EMG = demyelinating electrophysiologic features according to the criteria of the American Academy of Neurology (AAN) criteria; monoclonal population in bone marrow = monoclonal B- or plasma cell population in bone marrow aspiration; plasma cell, B cell = percentage of plasma cell, B cell infiltration in bone marrow biopsy.

Table 3 *Univariable analysis of the potential predictors for malignant transformation*

	MGUS, n = 88	Malignancy, n = 16	HR (95% CI)
Age at onset, mean (SD), y	59 (10)	56 (9)	1.0 (1.0–1.0)
Fatigue	20	40	2.9 (1.1–8.0)*
Bone pain	6	13	3.6 (0.9–14)*
Infections	1	0	0.7 (0.1–5.9)
Night sweats/unexplained fever	0	7	10.9 (2.0–60)†
Weight loss	11	20	74.1 (8–684)†
Progression of polyneuropathy	51	94	4.8 (0.8–36)*
IgG/IgA monoclonal gammopathy	38	21	2.0 (0.4–11)
Monoclonal protein level, mean (SD), g/L	2 (5)	11 (9)	1.1 (1.0–1.2)‡
Increasing monoclonal protein level	7	43	2.9 (1.0–8.3)‡
Anemia	14	50	121 (0.1–106267)
Anti-MAG antibodies	28	46	1.2 (0.4–3.9)

Values are percentages, unless otherwise specified, with hazard ratios (95% CI).

* $p < 0.1$.
† $p < 0.01$.
‡ $p < 0.05$.

MGUS = monoclonal gammopathy of undetermined significance; malignancy = hematologic malignancy; anemia = hemoglobin level < 12 g/L (<7.4 mmol/L) in women, < 14 g/L (<8.6 mmol/L) in men; anti-MAG antibodies = anti-myelin-associated-glycoprotein antibodies.

sweats, and M-protein level were independent prognostic variables significantly associated with malignant transformation (table 4). Among patients who had or who developed a hematologic malignancy, three patients died (pneumonia) compared to five patients of those without a malignancy (breast cancer, kidney cancer, pulmonary embolism after aortic bypass surgery, pneumonia, and cardiac disease, HR for mortality 8.3, 95% CI: 2.1 to 33.7). We did not find a difference in survival of patients with IgG/IgA or IgM type of the monoclonal gammopathy.

Discussion. In this prospective study of 193 patients with polyneuropathy associated with monoclonal gammopathy 34 patients were diagnosed with a hematologic malignancy at initial screening or during follow-up (18%). At diagnosis 9% of the patients with polyneuropathy associated with monoclonal gammopathy had an underlying hematologic malignancy. During 3 years of follow-up in 17 of the 176 remaining patients with polyneuropathy associated with MGUS malignant transformation occurred. The incidence of malignant transformation in polyneuropathy associated with MGUS (2.7/100 patient-years, 95% CI 1.52/100 to 4.22/100 patient years) appears to be higher than in MGUS without polyneuropathy (1/100 patient-years, 95% CI 0.85/100 to 1.24/100 patient years, $p < 0.05$).[5] Unexplained weight loss, progression of the polyneuropathy, unexplained fever or night sweats, and M-protein level were independent predictive factors of malignant transformation.

This study confirms the findings of our previous retrospective cohort study in which 22% of the patients with polyneuropathy associated with MGUS developed a hematologic malignancy during long-term follow-up.[12] The high frequency of hematologic malignancies could have been due to selection bias, because patients with polyneuropathy associated with monoclonal gammopathy and a progressive disease course may be referred earlier to a tertiary clinic than patients with slow progression of the dis-

Table 4 *Multivariable analysis of clinical and laboratory predictors of malignant transformation*

	Model 1	Model 2	Model 3
	Clinical determinants, HR (95% CI)	Laboratory determinants, HR (95% CI)	Clinical and laboratory determinants, HR (95% CI)
Weight loss	226 (12–4381)		226 (12–4381)
Progression of the polyneuropathy	118 (3.0–4638)		118 (3.0–4638)
Unexplained fever or night sweats	27 (1.8–403)		27 (1.8–403)
Monoclonal protein level (per 1 g/L)		1.1 (1.0–1.2)	1.0 (0.9–1.1)

Values are hazard ratios (95% CI).

ease. In addition, the high frequency of underlying hematologic malignancies could have been due to referral bias, since patients with a very slowly progressive polyneuropathy followed in a non-university hospital may not be screened for the presence of an M-protein and once they have a progressive polyneuropathy these patients are referred to an university hospital where the malignant monoclonal gammopathy is found. However, a high number of patients without a hematologic malignancy at initial screening developed a hematologic malignancy during prospective follow-up. To determine the incidence of and predictors for malignant transformation during follow-up, patients with polyneuropathy associated with MGUS were screened at regular intervals. The group of patients in the follow-up study for analyses of predictive factors included more patients with a progressive polyneuropathy and more patients with a hematologic malignancy than the group of patients not included. Patients without a progressive disease course were frequently lost to follow-up. This leads to under-representation of patients with chronic polyneuropathy in the analysis, and may affect the association of progression of the polyneuropathy and malignant transformation.

Several prognostic factors for malignant transformation for patients with MGUS without polyneuropathy have been reported in previous retrospective studies, i.e., M-protein level,[25,26] increase of M-protein level during follow-up, light-chain proteinuria, age $>$ 70 years,[27] kappa light chain,[26] and IgA isotype.[28] In the past 2 years, two large studies reported M-protein level as the most important independent predictor for malignant transformation in both IgG and IgM MGUS.[5,6] Patients with polyneuropathy associated with MGUS in this prospective multivariate study were comparable to patients with MGUS in the reported studies with respect to age, M-protein level, and bone marrow infiltration and we confirmed the findings in MGUS without polyneuropathy.[5,6] In addition to reported findings, we identified weight loss, unexplained fever or night sweats, and progression of the polyneuropathy as predictive factors for malignant transformation. This is important since specialists in neurology, hematology, and internal medicine should be aware of the underlying risk of a hematologic malignancy in patients with polyneuropathy associated with monoclonal gammopathy. Unexpectedly, the incidence of malignant transformation in patients with a demyelinating polyneuropathy associated with IgM anti-MAG antibodies is similar to the high incidence found in the total group of patients with polyneuropathy associated with MGUS. Also in the patients with anti-MAG antibodies, who normally have a slowly progressive disease course, progression of the polyneuropathy was associated with malignant transformation.[22,29]

Frequent bone marrow examination enables early detection of patients with a hematologic malignancy and may prevent serious complications by adequate timing of treatment. In this and other studies the neuropathy symptoms improved with the acknowledged therapy of the underlying malignancy.[18,30-32]

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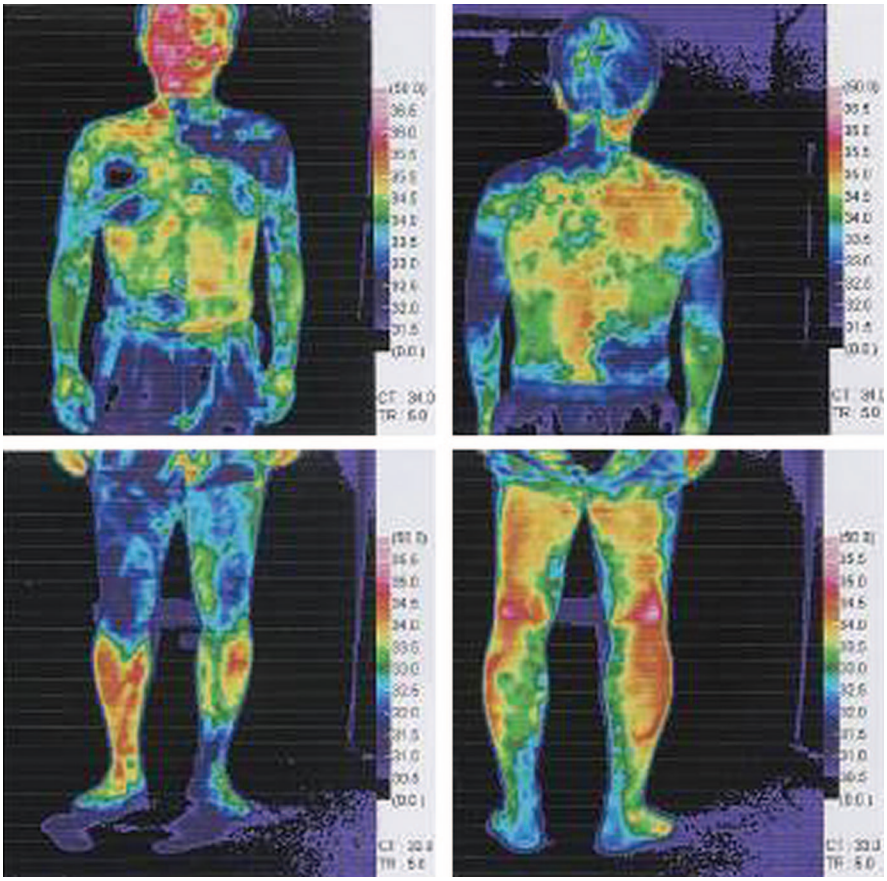

Figure. Thermography (Thermoviewer JTG 5310, JEOL Co., Japan) shows a "patchwork pattern" of body surface temperature distribution after exercise. Body surface temperature was higher in the anhidrotic area (red) than in the sweating area (blue).

Thermogram of idiopathic segmental anhidrosis

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A 45-year-old man presented with an 8-year history of left hemifacial hyperhidrosis induced by exercise or hot environments. He began to experience episodes of heat intolerance and noticed anhidrosis over the right face, right neck, left trunk, and right lower leg (figure). Physical, neurologic, and laboratory examinations revealed no abnormalities. He had no diabetes mellitus. Tonic pupils and hyporeflexia were absent. Idiopathic segmental anhidrosis (ISA) was diagnosed.[1] We consider that ISA is a forme fruste of Ross syndrome plus,[2] in which multiple lesions associated with sympathetic ganglion damage are suggested to occur.

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