Long-term Follow-up of 241 Patients With Monoclonal Gammopathy of Undetermined Significance: The Original Mayo Clinic Series 25 Years Later

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OBJECTIVE: **To determine the long-term outcome of patients with monoclonal gammopathy of undetermined significance (MGUS).**

PATIENTS AND METHODS: **We reviewed the medical records of 241 patients with MGUS who were examined at the Mayo Clinic in Rochester, Minn, between January 1, 1956, and December 31, 1970.**

RESULTS: **Follow-up was 3579 person-years (median, 13.7 years; range, 0-39 years). Only 14 patients (6%) were alive and had no substantial increase of M protein at last follow-up; 138 patients (57%) died without evidence of multiple myeloma or a related disorder; a malignant lymphoplasma cell proliferative disorder developed in 64 patients (27%). The interval from diagnosis of MGUS to diagnosis of multiple myeloma or related disorder ranged from 1 to 32 years (median, 10.4 years).**

CONCLUSIONS: **The median survival rate of study patients with MGUS was only slightly shorter than that of a comparable US population. Risk of progression of MGUS to lymphoplasma cell malignancy is indefinite and persists even after more than 30 years of follow-up, with no reliable predictors of malignant evolution.**

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Monoclonal gammopathy of undetermined significance (MGUS) is defined by the presence of a serum M protein value of 3.0 g/dL or less; no M protein or only small amounts of monoclonal light chain in the urine; the absence of lytic bone lesions, anemia, hypercalcemia, or renal insufficiency related to the M protein; and, if determined, a proportion of plasma cells in the bone marrow of 10% or less.[1,2] Among 1056 newly recognized patients with an M protein at the Mayo Clinic in 2002, 626 (59%) had MGUS, which is common and reported in approximately 3% of persons older than 70 years.[3-7] These patients are attended by various physicians in many fields of clinical practice, including family practitioners, internists, neurologists, dermatologists, and surgeons. Thus, MGUS has widespread occurrence, and both patients and physicians would benefit from knowing whether the presence of an M protein will remain stable and benign or will progress to multiple myeloma, amyloidosis, macroglobulinemia, or a related lymphoplasma cell proliferative process. In an effort to ascertain the outcome of MGUS, we studied 241 patients examined at the Mayo Clinic between 1956 and 1970.[1,8,9] We describe follow-up of this cohort for up to 47 years.

PATIENTS AND METHODS

We reviewed the medical records of all 241 patients with monoclonal gammopathy who were examined at the Mayo Clinic in Rochester, Minn, between January 1, 1956, and December 31, 1970. The study was approved by the Mayo Foundation Institutional Review Board in conformity with the Helsinki protocol. Patients with multiple myeloma, systemic amyloidosis, macroglobulinemia, and other lymphoproliferative disorders were excluded. Follow-up data were accumulated through April 15, 2003. Patients who had not been to the Mayo Clinic within 1 year were asked to send a sample of serum and any laboratory data that had been obtained in the interim. Those in whom the M protein value had increased were asked to send an aliquot from a 24-hour urine specimen. Electrophoresis and immunoelectrophoresis or immunofixation were performed on serum and urine specimens.[10] The IgG subclass was identified and quantitated by radioimmunoassay.[11]

Patients were classified a posteriori into 1 of 4 groups: group 1, patients still living without an increase in serum M protein value during follow-up; group 2, patients in whom the M protein value had increased to 3.0 g/dL or higher but who had not required chemotherapy for their lymphoplasma cell proliferative disorder; group 3, patients who died of unrelated causes; and group 4, patients in whom multiple myeloma, amyloidosis, macroglobulinemia, or a related lymphoplasma cell proliferative disorder had developed.

The primary end points of progression and survival were estimated by using the Kaplan-Meier method.[12] Curves were compared by using the log-rank test.[13] Expected survival rate was based on that of the US population

TABLE 1. **Hemoglobin Value, Serum M Protein Concentration, and Percentage of Plasma Cells in Bone Marrow at Diagnosis of MGUS***

| | Patient group | | | | |
	1 (n=14)	2 (n=25)	3 (n=138)	4 (n=64)	Total (N=241)
Hemoglobin (g/dL)					
Median	13.7	12.9	13.2	13.2	13.2
Range	10.1-16.6	8.4-15.5	7.4-16.5	9.7-16.5	7.4-16.6
Serum M protein (g/dL)					
Median	1.7	2.0†	1.7	1.7	1.7
Range	1.2-3.0	1.2-2.7	0.3-3.2	0.9-2.6	0.3-3.2
Plasma cells (%)					
Median	3.0	3.0	3.0	3.5	3.0
Range	1.0-5.0	1.0-6.0	1.0-10.0	1.0-7.0	1.0-10.0

*The patient groups are described in the "Patients and Methods" section. MGUS = monoclonal gammopathy of undetermined significance.
†P=.002, but this is of doubtful biologic significance.

with use of 1930-2000 decennial life tables, with each patient matched to the control population by age, sex, and date of entry. Calculations were based on the method of Hakulinen.[14] The effects of potential risk factors on the outcome of progression were evaluated with Cox proportional hazards models.[15] Comparisons of baseline clinical factors among the 4 groups were performed with χ^2 tests[16] for discrete nominal variables and with 1-way analysis of variance[17] for variables with continuous distributions. All statistical tests were 2-sided, and the threshold for statistical significance was P=.05. All analyses were performed with use of SAS version 8.2 (SAS Institute Inc, Cary, NC) and S-PLUS version 6.1 (Insightful Corp, Seattle, Wash).

RESULTS

CLINICAL AND LABORATORY FEATURES AT DIAGNOSIS OF MGUS

Sixty-three patients (26%) came to the Mayo Clinic for general physical examinations and had no diagnosis other than MGUS. Cardiovascular or cerebrovascular disease was present in 13%. Inflammatory disorders were found in 26 patients, 4 had fever of undetermined origin that had been present intermittently for 4 to 22 years, 3 had recurrent phlebitis, 2 had chronic inflammatory bowel disease, and 1 had sprue. Sixteen patients had a malignant neoplasm, including acute leukemia and Kaposi sarcoma (1 each). Connective tissue disorders were diagnosed in 14 patients. Lupus erythematosus was present in 3, scleroderma in 3, ankylosing spondylitis in 2, rheumatoid arthritis in 1, and unclassified connective tissue disease in 5. Five patients had carpal tunnel syndrome but no evidence of systemic amyloidosis. Of the 9 patients with hematologic disorders, 2 had myelofibrosis with myeloid metaplasia, 2 had idiopathic thrombocytopenic purpura, and 1 each had von Willebrand disease, hypoplastic anemia, red cell apla-

sia, undifferentiated myeloproliferative disease, and idiopathic neutropenia. Of the 9 patients with endocrine disorders, 3 had hyperparathyroidism, 3 had osteoporosis, and 1 each had Cushing disease, Graves disease, and Turner syndrome. Miscellaneous disorders included psychoneurosis, hyperventilation syndrome, duodenal ulcer, melena, pruritus, diabetes, Peyronie disease, and plane xanthomatosis.

The cohort consisted of 140 male patients (58%) and 101 female patients (42%) with a median age of 64 years when MGUS was diagnosed. One third were aged 70 years or older, and only 4% were younger than 40 years when M protein was recognized. These patients were followed up for 3579 person-years (median, 13.7 years per patient; range, 0-39 years). All patients except 1 were followed up within 1 year of the writing of this article. No patients were lost to follow-up. Only 16 patients were still alive, 14 in group 1 (patients living with stable M protein values) and 2 in group 4 (patients in whom multiple myeloma or a related disorder developed).

The liver was palpable in 15% of the 241 patients, and the spleen was palpable in 4%. In patients whose liver was palpable 5 cm or more below the costal margin, the causes were congestive heart failure, biliary cirrhosis, hemochromatosis, and fatty liver. Splenomegaly more than 5 cm below the costal margin resulted from myelofibrosis and myeloid metaplasia, undifferentiated myeloproliferative disease, and lupus erythematosus; in 2 patients, no cause was apparent.

The initial hemoglobin value ranged from 7.4 to 16.6 g/dL (Table 1). In 9 patients with hemoglobin values less than 10 g/dL, the causes were melena, myeloid metaplasia, myeloproliferative disease, Wegener granulomatosis, hypoplasia of the bone marrow, chronic cold agglutinin disease, nutritional anemia, biliary cirrhosis, and hypernephroma. The leukocyte count was less than 2×10^9/L in 1

patient who had lupus erythematosus; it exceeded 20×10^9/L in 2 patients, 1 with an undifferentiated myeloproliferative process and 1 with myeloid metaplasia. In 5 patients with platelet counts less than 100×10^9/L, the causes were myeloid metaplasia, acute leukemia, idiopathic thrombocytopenic purpura, cryoglobulinemia, and hypoplasia of the bone marrow. Thrombocytosis (platelet count, $>500 \times 10^9$/L) occurred in 2 patients, 1 with pneumonia and 1 with rectal bleeding. Renal insufficiency with a serum creatinine level of more than 2.0 mg/dL was present in 5 patients; 3 had nephrosclerosis, 1 had diabetes mellitus, and 1 had uric acid nephropathy. The serum albumin value was less than 2.0 g/dL in 2 patients, 1 with Wegener granulomatosis and 1 with a hypernephroma. Only 2 patients had hypercalcemia (calcium level, >11.0 mg/dL); both had hyperparathyroidism.

Two patients had a broad-based polyclonal-appearing band, and 3 others had no discrete measurable band; all 5 had an M protein apparent on immunoelectrophoresis. The serum M protein value ranged from 0.3 to 3.2 g/dL (Table 1). IgG accounted for 73.5%; IgA, 10.5%; and IgM, 14%; 2% had a biclonal gammopathy. The light chain was κ in 63% and λ in the remainder. The subclass was IgG1 in 87% of those with an IgG monoclonal gammopathy. Electrophoretic mobility of the M protein and its heavy-chain type and light-chain class remained unchanged throughout the observation period. A reduction of uninvolved immunoglobulins was found in 63 of 164 patients tested (38%) (Table 2). Only 7 patients had a urinary monoclonal light chain (κ in 4, λ in 3) at or before the time serum M protein was detected.

The median percentage of bone marrow plasma cells in the 109 patients in whom a bone marrow aspirate was obtained at the time M protein was detected was 3% (range, 1%-10%) (Table 1).

GROUP 1: PATIENTS LIVING WITH STABLE M PROTEIN VALUES

The number of living patients whose M protein value remained stable decreased from 46 in 1993 to 14 (6%) in 2003 (Table 3). The median duration of follow-up in this subgroup was 33 years (range, 31-39 years). The hemoglobin concentration, serum M protein value, type of serum heavy and light chains, reduction in uninvolved immunoglobulins, subclass of IgG heavy chain, and number of plasma cells in the bone marrow in this group of patients with a stable M protein value did not differ substantially from these features in the overall study group. One male patient had a documented κ urinary protein of more than 1.0 g/24 h for 39 years and had had grade 3 to grade 4 proteinuria for 7 years before; thus, the total duration of proteinuria was 46 years. His creatinine level had increased from 1.4 to 2.3 mg/dL, but he remained asymptomatic.

TABLE 2. **Reduction of Uninvolved Immunoglobulins in Patients With MGUS***

	Patient group				
	1 (n=14)	2 (n=25)	3 (n=138)	4 (n=64)	Total (N=241)
No. of patients tested	10	17	95	42	164
No. (%) with reduction	3 (30)	6 (35)	33 (35)	21 (50)	63 (38)

*The patient groups are described in the "Patients and Methods" section. MGUS = monoclonal gammopathy of undetermined significance.

GROUP 2: PATIENTS WITH INCREASED M PROTEIN VALUES

During follow-up, 25 patients had a serum M protein value of 3.0 g/dL or higher but did not require chemotherapy for multiple myeloma, macroglobulinemia, or amyloidosis (Table 3). The median duration of follow-up in this group was 19 years (range, 2.9-39.0 years). The median duration of follow-up before the M protein value reached 3.0 g/dL was 9.5 years (range, 2.0-38.6 years). These patients were followed up for an additional median 7.1 years (range, 0-19.2 years) after development of an M protein value of 3.0 g/dL or more but did not develop symptomatic myeloma or macroglobulinemia.

All 25 patients in group 2 died; 5 died of infection, 5 of cardiac-related causes, 3 of renal insufficiency, 2 each of carcinoma and cerebrovascular disease, 6 of other causes, and 2 of unknown causes.

GROUP 3: PATIENTS WHO DIED OF UNRELATED CAUSES

The 138 patients in this group died without evidence of symptomatic multiple myeloma, amyloidosis, macroglobulinemia, or other lymphoproliferative disease. The median interval from recognition of serum M protein to death was 9 years (range, 0-36 years). Sixty-five patients survived more than 10 years after serum M protein was detected. Two patients had a monoclonal urinary light chain when

TABLE 3. **Course of 241 Patients With MGUS***

Patient group	Description	No. (%) of patients at follow-up†
1	Living patients with no substantial increase of M protein level	14 (6)
2	M protein level ≥3.0 g/dL but no multiple myeloma or related disorder	25 (10)
3	Died of unrelated causes	138 (57)
4	Developed multiple myeloma, macroglobulinemia, amyloidosis, or related disorder	64 (27)

*The patient groups are described in the "Patients and Methods" section. MGUS = monoclonal gammopathy of undetermined significance.
†Person-years of follow-up = 3579 (median, 13.7 years per patient; range, 0-39 years).

TABLE 4. **Development of Multiple Myeloma or Related Disorder in 64 Patients With MGUS***

	No. (%) of patients	Interval to disease (y)	
		Median	Range
Multiple myeloma	44 (69)	10.6	1-32
Macroglobulinemia	7 (11)	10.3	4-16
Amyloidosis	8 (12)	9.0	6-19
Lymphoproliferative disease	5 (8)	8.0	4-19
Total	64 (100)	10.4	1-32

*MGUS = monoclonal gammopathy of undetermined significance.

serum M protein was recognized. In 19 patients, a monoclonal urinary light chain was recognized during follow-up; however, because immunoelectrophoresis was not performed when MGUS was recognized, urinary M protein may have been present at diagnosis.

In this group, cardiac disease was the most frequent cause of death (49 patients), followed by cerebrovascular disease (18 patients). Sixteen patients died of a non–plasma cell malignancy.

GROUP 4: PATIENTS IN WHOM MULTIPLE MYELOMA OR A RELATED DISORDER DEVELOPED

Multiple myeloma, primary amyloidosis, macroglobulinemia, or a related malignant lymphoproliferative disorder developed in 64 patients (27%) (Table 4). The patients in this group were followed up for a median of 14 years (range, 3-35 years) before diagnosis of a serious lymphoplasma cell proliferative disorder. The actuarial rate of disease development was 17% at 10 years, 34% at 20 years, and 39% at 25 years, a rate of approximately 1.5% per year (Figure 1).
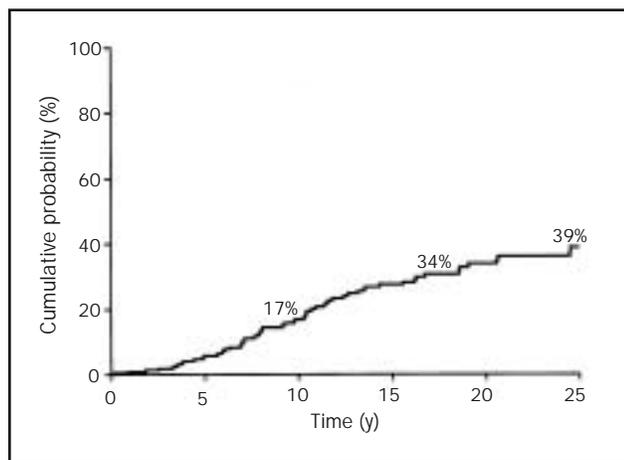

FIGURE 1. Rate of development of multiple myeloma or related disorder in 241 patients with monoclonal gammopathy of undetermined significance.

On the basis of the proportional hazards model, no statistically significant relationship was seen between age, sex, hemoglobin level, serum M protein level, presence of urinary light chain, number of bone marrow plasma cells, class of heavy chain, type of monoclonal light chain, serum creatinine level, or albumin level and the development of multiple myeloma, amyloidosis, macroglobulinemia, or a related lymphoproliferative disorder.

Of the 64 patients in this group, 44 (69%) had multiple myeloma. Bone marrow aspirate or biopsy specimens contained 15% or more abnormal plasma cells in all but 4 patients. Two of the 4 patients were diagnosed as having multiple myeloma at their home hospital, and we were unable to obtain the results of bone marrow studies. Both patients had extensive lytic lesions and severe anemia. The third patient had a large destructive plasmacytoma of the sacrum, stenosis of the spinal canal, and a serum M protein spike of 3.4 g/dL, but we could not obtain results of the bone marrow study. The fourth patient had severe anemia, hypercalcemia, and an M protein spike of 3.7 g/dL but refused a bone marrow examination.

The serum M protein spike was more than 3.0 g/dL in 33 of the 44 patients. Three of the 11 patients with a serum M protein spike of less than 3.0 g/dL had a high urinary M protein level (Bence Jones proteinuria), and 7 had skeletal involvement. In all but 1 patient, the serum M protein spike increased when multiple myeloma developed; the patient who was the exception had severe back pain, extensive skeletal involvement, and bone marrow containing 25% plasma cells. Of the patients who underwent assessment, 2 had a monoclonal urinary light chain at the time of diagnosis. Of the 44 patients with multiple myeloma, 30 (68%) had lytic lesions or fractures, and 3 others had osteoporosis. These findings are typical for multiple myeloma; thus, the criteria for the diagnosis of multiple myeloma were readily fulfilled.

The interval from diagnosis of MGUS to diagnosis of multiple myeloma ranged from 1 to 32 years (median, 10.6 years). In 10 patients, the diagnosis of multiple myeloma was made more than 20 years after serum M protein was detected. Median survival after diagnosis of multiple myeloma was 33 months, and only 1 patient is still alive.

The mode of development of multiple myeloma was variable. In 14 patients, the serum M protein value remained stable for 4 to 29 years and then gradually increased to symptomatic multiple myeloma during a 1- to 7-year period. In 9 patients, the serum M protein value was stable for 2 to 28 years and then increased in less than 1.5 years as myeloma developed. In 7 patients, the serum M protein value was stable for 1 to 16 years, followed by intervals of 2 to 10 years without serum studies before multiple myeloma was diagnosed. Seven patients had fluc-

tuating but gradually increasing serum M protein spikes until multiple myeloma was diagnosed 5 to 29 years later. In 7 patients, no serum specimens were available between the time of detection of the serum M protein and the diagnosis of multiple myeloma 3 to 10 years later.

Systemic amyloidosis was found in 8 patients, 6 to 19 years (median, 9 years) after serum M protein was detected. Amyloidosis was noted at autopsy in 3 patients, on renal biopsy in 2, on rectal biopsy in 1, on lymph node biopsy in 1, and as an incidental finding at the time of operation for carcinoma of the colon in 1. The initial manifestation of amyloidosis was nephrotic syndrome (2 patients); cardiomegaly (1); acute pulmonary edema (1); fatigue, diarrhea, and weight loss of 13.6 kg (1); lymphadenopathy and weight loss (1); and peripheral neuropathy (1). Amyloidosis was not clinically suspected in the 3 patients in whom the diagnosis was made at autopsy and would have been undiagnosed if a postmortem examination had not been performed. One of these patients came to the emergency department with acute pulmonary edema and died; in another patient, weakness, weight loss, and gastrointestinal tract symptoms had developed for which no cause was found until autopsy; the third patient had symptomatic type I cryoglobulinemia, sensorimotor peripheral neuropathy, and congestive heart failure.

Waldenström macroglobulinemia developed in 7 patients 4 to 16 years (median, 10.3 years) after M protein was detected. These patients all had serum values of IgM κ protein that ranged from 3.1 to 8.5 g/dL during the course of disease. One patient had a biclonal gammopathy (IgM κ and IgA κ), but only the IgM κ component increased. All 7 patients had anemia (5 had hemoglobin values ≤10.0 g/dL), and their bone marrow aspirates and biopsy or autopsy specimens showed increased numbers of lymphocytes and plasma cells. Median survival was 6.5 years.

In 5 patients, a malignant lymphoproliferative process developed 4 to 19 years (median, 8 years) after M protein was detected. In 1 patient, chronic lymphocytic leukemia that necessitated chemotherapy occurred after 9.5 years. Four courses of chlorambucil were given for recurrent lymphocytosis, but the IgM κ protein remained stable for 19 years. One patient with lupus erythematosus had a biclonal gammopathy (IgG λ and IgM κ); 9 years later, an aggressive, diffuse, undifferentiated malignant lymphoma developed, and the patient died. In another patient, a malignant lymphoproliferative process and symptomatic anemia developed at 20 years. One patient had diffuse mixed lymphoma of the jejunum discovered during surgical exploration for abdominal pain 10 years after serum M protein was detected; during the 23-year follow-up, no recurrence has been noted. In the fifth patient, fever, night sweats, and fatigue developed 22 years after an IgM monoclonal

gammopathy was detected; 3 months later, an aggressive lymphoma of the retroperitoneum, bone marrow, and central nervous system resulted in death. Only 1 of the 5 patients with a malignant lymphoproliferative process had an associated increase in monoclonal gammopathy.

ANALYSIS BY IMMUNOGLOBULIN GROUP

In the current study, 64 of 241 patients (27%) had multiple myeloma, amyloidosis, macroglobulinemia, or other lymphoproliferative disease during follow-up. The rate of development of these diseases among the 202 patients with an IgG or IgA protein was 15% at 10 years, 30% at 20 years, and 44% at 30 years. Among the 34 patients with an IgM monoclonal gammopathy, the actuarial rate for the development of these diseases was 23% at 10 years, 52% at 20 years, and 52% at 30 years. The actuarial risk of development of multiple myeloma or related disorder did not differ significantly, whether the M protein was IgG, IgA, or IgM (Figure 2). Survival of patients with an IgG, IgA, or IgM M protein was also similar (Figure 3). Distribution of the types of multiple myeloma or related disorder associated with the type of serum M protein is shown in Table 5. In 25 additional patients, an M protein value of 3.0 g/dL or higher developed but no multiple myeloma or related disorder (group 2). In summary, either multiple myeloma or a related disorder or a serum M protein value of 3.0 g/dL or higher (but no multiple myeloma or related disorder) developed in 89 of the 241 patients (37%) (Table 6).

SURVIVAL RATE COMPARED WITH THAT OF THE US POPULATION

The expected survival rate of patients with MGUS was compared with that for the US population with use of 1930-2000 decennial life tables, with each patient matched to the control population by age, sex, and date of entry. The comparison revealed only a slightly shorter survival rate for the 241 patients with MGUS (Figure 4).

DISCUSSION

Distinguishing between patients with MGUS and those in whom multiple myeloma or a related disorder will eventually develop is difficult when MGUS is recognized initially. Knowing the serum M protein value is useful because higher levels are associated with a greater likelihood of progression.[18,19] A serum M protein level of more than 3.0 g/dL usually indicates symptomatic multiple myeloma or macroglobulinemia, but some exceptions exist such as smoldering myeloma or macroglobulinemia.[20] The levels of the immunoglobulin class not associated with the presence of M protein (normal polyclonal or background immunoglobulins) may help distinguish benign from malignant gammopathies. However, 91% of 1027 patients with
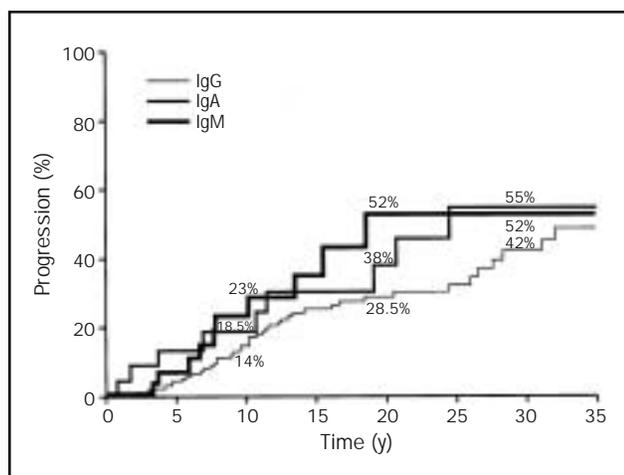
FIGURE 2. Rate of development of multiple myeloma or related disorder in 241 patients with monoclonal gammopathy of undetermined significance stratified by immunoglobulin class (*P*=.08).
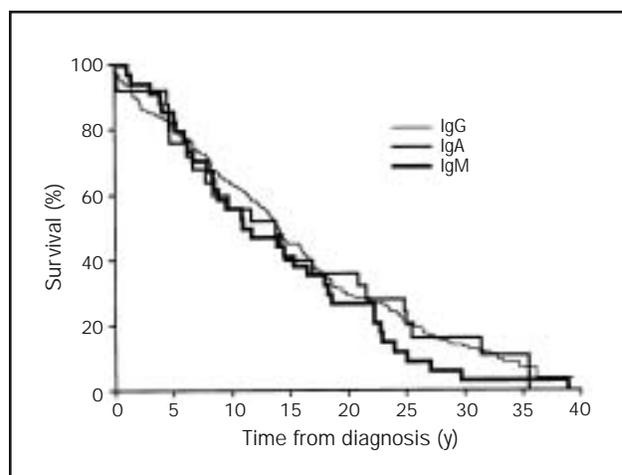

FIGURE 3. Survival rates of 241 patients with monoclonal gammopathy of undetermined significance stratified by heavy-chain immunoglobulin class (*P*=.29).

myeloma had a reduction in 1 or more uninvolved immunoglobulins, and uninvolved immunoglobulins were reduced in 38% of 840 patients whose immunoglobulin concentrations were determined quantitatively.[19] One or more uninvolved immunoglobulins were reduced in 63 of 164 tested patients (38%) with MGUS in this series. Peltonen et al[21] reported that uninvolved immunoglobulins were decreased in 88% of patients with a lymphocytic or plasmacytic neoplasm but also were reduced in 38% of patients with benign monoclonal gammopathy.

The association of a monoclonal light chain (Bence Jones proteinuria) with a serum M protein suggests a neoplastic process. Nonetheless, monoclonal light chains have been found in the urine of patients with benign or stable monoclonal gammopathies.[22-24] The presence of the monoclonal light chain in the 1384 patients from southeastern Minnesota did not predict progression.[19]

The number of bone marrow plasma cells may be helpful in predicting progression. In 1 series, the transformation rate was 6.8% when the bone marrow plasma cell level was less than 10% and was 37% in those patients with a bone marrow plasma cell level of 10% to 30%.[25] In another

study, the existence of more than 5% bone marrow plasma cells was an independent risk factor for progression of MGUS.[26] The number of bone marrow plasma cells was not useful in the current study, but the number of patients examined was small.

Patients with MGUS with an IgM or IgA M protein had a higher risk of progression than did those with an IgG M protein in the southeastern Minnesota study.[19] In the Bladé et al series,[27] patients with an IgA M protein had a higher probability of developing multiple myeloma. The type of M protein had no predictive value in the current study, but the number of patients examined was small.

The plasma cell labeling index is a measurement of the synthesis of DNA and helps in the differential diagnosis of multiple myeloma. However, approximately one third of patients with symptomatic multiple myeloma have a normal plasma cell labeling index.[28] The presence of circulating plasma cells in the peripheral blood is associated with active myeloma, whereas patients with MGUS or smoldering multiple myeloma have few or no circulating plasma cells.[29] The plasma cell labeling index and the detection of circulating plasma cells in the peripheral blood were un-

TABLE 5. **Type of Multiple Myeloma or Related Disorder in 64 Patients With MGUS***

Type of immunoglobulin	No. of patients	Type of disease			
		Multiple myeloma	Amyloidosis	Macro-globulinemia	Lymphoproliferative disease
IgA	9	8	1	0	0
IgG	42	36	5	0	1
IgM	10	0	1	6	3
Biclonal	3	0	1	1	1
Total	64	44	8	7	5

*MGUS = monoclonal gammopathy of undetermined significance.

TABLE 6. **Development of Multiple Myeloma or Related Disorder or Increase of M Protein Values in 241 Patients With MGUS***

Type of immunoglobulin	No. of patients	No. (%) with multiple myeloma or related disorder	No. (%) with M protein ≥3.0 g/dL but no multiple myeloma or related disorder	Total No. (%)†
IgA	25	9 (36)	0 (0)	9 (36)
IgG	177	42 (24)	19 (11)	61 (34)
IgM	34	10 (29)	5 (15)	15 (44)
Biclonal	5	3 (60)	1 (20)	4 (80)
Total	241	64 (27)	25 (10)	89 (37)

*MGUS = monoclonal gammopathy of undetermined significance.
†With multiple myeloma or related disorder and/or with M protein ≥3.0 g/dL.

available for this series of patients whose MGUS was diagnosed between 1956 and 1970.

The presence of normal polyclonal plasma cells is associated with MGUS.[30] Serum levels of interleukin 6 are frequently elevated in patients with multiple myeloma.[31] Interleukin 1β is produced by plasma cells in almost all patients with multiple myeloma but is undetectable in most patients with MGUS.[32] Bone marrow angiogenesis is increased in multiple myeloma in contrast to MGUS; however, it should be remembered that one third of patients with multiple myeloma do not have increased angiogenesis.[33] Magnetic resonance imaging scans are normal in patients with MGUS, whereas almost 90% of patients with multiple myeloma have abnormal scans.[34] Conventional cytogenetic studies are not useful in distinguishing MGUS from multiple myeloma because abnormal karyotypes rarely are seen in patients with MGUS. β_2-Microglobulin levels, presence of J chains in malignant plasma cells, acid phosphatase levels in plasma cells, reduction of T4 cells, and telomerase activity are not useful in distinguishing patients with MGUS from those with multiple myeloma.

Thus, no laboratory values or clinical features permit the clinician to determine whether MGUS in an individual patient will progress. The only certain approach is to monitor changes in the serum M protein level. If a patient has no features of myeloma or amyloidosis and the serum M protein level is less than 1.5 g/dL, serum protein electrophoresis should be repeated annually. Bone marrow examination and skeletal radiography are seldom necessary in this situation. If the asymptomatic patient has an M protein level of 1.5 to 2.0 g/dL, the IgG, IgA, and IgM levels should be measured and a 24-hour urine specimen should be collected for electrophoresis and immunofixation as a baseline. Serum protein electrophoresis should be repeated 6 months later and, if stable, should be repeated annually or sooner if symptoms develop. If the IgG or IgA M protein level is higher than 2.0 g/dL, a metastatic bone survey, including views of the humeri and femurs, should be performed in addition to a bone marrow aspirate and biopsy. If

possible, cytogenetic studies and a search for circulating plasma cells in the peripheral blood should be performed and the plasma cell labeling index determined.

If the patient has an IgM M protein level higher than 2.0 g/dL, aspiration and biopsy of the bone marrow and computed tomography of the abdomen may be useful for recognizing macroglobulinemia or a related lymphoproliferative disorder. If results of these studies are satisfactory, serum protein electrophoresis should be repeated 3 to 6 months later; if results are stable, the test should be repeated every 6 to 12 months.

CONCLUSIONS

Distinguishing between MGUS and multiple myeloma is based on clinical and laboratory factors such as symptoms, anemia, hypercalcemia, renal insufficiency, and lytic bone lesions. In the current series of 241 patients with MGUS, the initial hemoglobin value, amount of serum M protein,
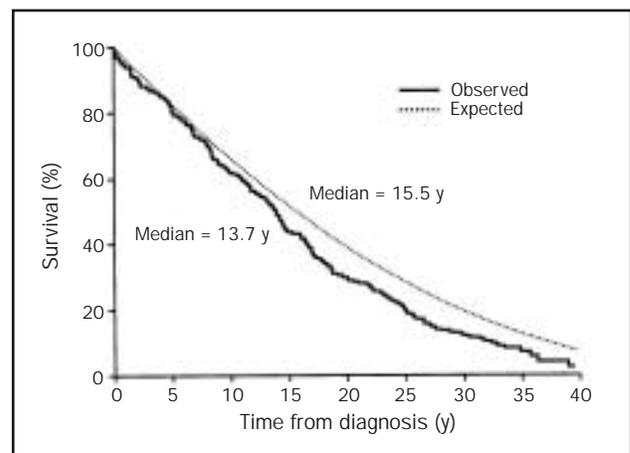
FIGURE 4. Survival rate of 241 patients with monoclonal gammopathy of undetermined significance compared with expected survival rate of the US population using 1930-2000 decennial life tables.

number of plasma cells in the bone marrow, and levels of normal immunoglobulins did not differ substantially between those whose conditions progressed and those whose conditions remained stable. Analysis of age, sex, presence of organomegaly, presence of small amounts of monoclonal light chain in the urine, serum albumin level, and IgG subclass did not initially allow a distinction to be made between patients with MGUS and those in whom lymphoplasma cell proliferative disorders ultimately developed.

No single test can reliably distinguish a patient with MGUS from one in whom symptomatic myeloma or other malignant lymphoplasma cell proliferative disorder will develop. The most reliable means of distinguishing a stable course from a progressive course is the serial measurement of the M protein in the serum and urine and periodic reevaluation of clinical and laboratory studies to determine whether multiple myeloma, systemic amyloidosis, macroglobulinemia, or other malignant lymphoplasma cell proliferative disorder has developed. Furthermore, the median survival rate of the 241 patients with MGUS was only slightly shorter than that of a comparable US population.

This study shows that the risk of progression of MGUS to plasma cell malignancy is indefinite and persists even after more than 30 years of follow-up.

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