Long-term Follow-up of IgM Monoclonal Gammopathy of Undetermined Significance*

Short Title: Long-term Follow-up of IgM MGUS

Scientific Heading: Neoplasia

Robert A. Kyle, MD
Terry M. Therneau, PhD
S. Vincent Rajkumar, MD
Ellen D. Remstein, MD
Janice R. Offord, BS
Dirk R. Larson, MS
Matthew F. Plevak, BS
L. Joseph Melton III, MD

From the Division of Hematology and Internal Medicine (R.A.K., S.V.R.), the Division of Biostatistics (T.M.T, J.R.O., D.R.L., M.F.P.), the Division of Anatomic Pathology (E.D.R.), and the Division of Epidemiology (L.J.M.), Mayo Clinic, Rochester, Minnesota.

Address reprint requests to Robert A. Kyle, MD, Division of Hematology and Internal Medicine, Mayo Clinic, 200 First Street SW, Rochester, MN 55905.

*Supported in part by research grant CA 62242 from the National Cancer Institute.
Abstract

Little effort has been made to quantitate adverse outcomes of monoclonal gammopathy of undetermined significance (MGUS) of the IgM class, which progresses to lymphoma or Waldenström macroglobulinemia, whereas IgA and IgG MGUS progress to multiple myeloma, primary amyloidosis (AL), or a related plasma cell disorder. From 1960-1994, IgM MGUS was diagnosed in 213 patients in southeastern Minnesota. The end point was progression to lymphoma or a related disorder, as assessed with the Kaplan-Meier method. The 213 patients were followed for 1,567 person-years (median, 6.3 years per subject). Lymphoma developed in 17 patients (relative risk [RR], 14.8), Waldenström macroglobulinemia in 6 (RR, 262), primary amyloidosis in 3 (RR, 16.3), and chronic lymphocytic leukemia in 3 (RR, 5.7). The relative risk of progression was 16-fold higher in the patients with IgM MGUS than in the white population of the Iowa Surveillance, Epidemiology, and End Results Program. Cumulative incidence of progression was 10% at 5 years, 18% at 10 years, and 24% at 15 years. On multivariate analysis, the concentration of the serum monoclonal protein and level of serum albumin at diagnosis were the only risk factors for progression to lymphoma or a related disorder. Risk of progression to lymphoma or a related disorder at 10 years after the diagnosis of MGUS was 14% with an initial monoclonal protein value of 0.5 g/dL or less, 26% with 1.5 g/dL, 34% for 2.0 g/dL, and 41% for more than 2.5 g/dL.

Key words: follow-up; IgM; MGUS; monoclonal gammopathy

E-mail address: kyle.robert@mayo.edu
Introduction

Monoclonal gammopathy of undetermined significance (MGUS) is found in more than 2% of persons 50 years or older and in approximately 3% of those older than 70 years.\(^1\) MGUS is defined by the presence of a serum monoclonal protein (M protein) value less than 3 g/dL; no M protein or only small amounts of monoclonal light chains in the urine; absence of lytic bone lesions, anemia, hypercalcemia, and renal insufficiency related to the M protein; and less than 10% plasma cells in the bone marrow (if tested).\(^6,7\) This condition is clinically significant because of the high likelihood that some patients will have progression to multiple myeloma or some other plasma cell malignancy.\(^8\) Among patients with MGUS, 15% to 20% have the IgM subclass. Little effort has been made to determine the nature and frequency of adverse outcomes of MGUS of the IgM class, which has different clinical features and progresses to lymphoma or Waldenström macroglobulinemia rather than multiple myeloma.\(^9\)\(^-\)\(^13\)

Among 242 patients with MGUS of the IgM type recognized at Mayo Clinic from 1956-1978, a malignant lymphoid disorder developed in 40 (17%) an average of 4 years after recognition of the M protein.\(^9\) These disorders included Waldenström macroglobulinemia in 22 patients, lymphoproliferative disorder in 9, lymphoma in 6, primary amyloidosis (AL) in 2, and chronic lymphocytic leukemia in 1. In addition, 9 of the patients with MGUS had an increase in serum M protein of more than 0.5 g/dL, and 10 others had an increase of more than 1 g/dL. Of these 19 patients with an increase in M protein, none had development of symptomatic Waldenström macroglobulinemia or a related disorder.\(^9\) In larger series of MGUS, the IgM type has not been evaluated as a separate entity.\(^8\)\(^,\)\(^14\)\(^,\)\(^15\)
Therefore, our current knowledge is limited by the small numbers of patients and the modest follow-up in most series. Furthermore, most of the reports emanate from tertiary medical centers, where the results may be distorted by selective referral of patients at greater risk for adverse outcomes. Consequently, we evaluated the prognosis and predictors of outcome in a cohort of patients with IgM MGUS from southeastern Minnesota. We previously reported on 1,384 patients in southeastern Minnesota with IgG, IgA, and IgM MGUS, but the current analysis is restricted to the 214 patients with MGUS of the IgM class. Because IgM monoclonal gammopathies have different features and different outcomes, we believe that it is important to evaluate a large cohort of patients with IgM MGUS who have long-term follow-up in order to quantify their prognosis more accurately.

Methods

From January 1, 1960, through December 31, 1994, MGUS of the IgM class was diagnosed in 213 Mayo Clinic patients who resided in the 11 counties (including Olmsted County) of southeastern Minnesota. All patients had an IgM M protein value less than 3 g/dL at diagnosis. The M proteins were identified by cellulose acetate or agarose gel electrophoresis. If there was an abnormal band or equivocal pattern, immunoelectrophoresis or immunofixation was performed. Patients with smoldering macroglobulinemia, lymphoma, or related disorders at the time of recognition of the IgM M protein were excluded. The medical records linkage system of the Rochester Epidemiology Project makes possible the complete ascertainment of clinically diagnosed cases among Olmsted County residents. The 1980 population of Olmsted County was 92,006, and...
312,559 people resided in the remaining 10 counties of southeastern Minnesota in that year. We obtained a waiver of consent from the Institutional Review Board for these studies.

The primary end point of the study was progression to lymphoma or related disorders. Patients with an M protein were advised to undergo serum protein electrophoresis annually and were contacted if they did not. In addition, follow-up included review of each person’s inpatient and outpatient medical record at Mayo Clinic and review of death certificates for all who died. The end points with respect to progression to lymphoma or a related malignancy were calculated in terms of both cumulative probability and cumulative incidence of progression. The cumulative probability was calculated with a Kaplan-Meier estimate, in which the data on patients who died were censored; curves were compared with the log-rank test. The cumulative incidence curve, however, explicitly accounted for other causes of death and was computed with the method of Gooley et al. The effects of potential risk factors on progression rates were examined in a Cox proportional hazards model.

The risk of progression to each disease also was assessed relative to the risk in the general population by applying age- and sex-specific incidence rates for these conditions in the white cohort from the Iowa Surveillance, Epidemiology, and End Results Program to the age-, sex-, and calendar year-specific person-years of follow-up in our study cohort. The confidence intervals for the relative risks are based on a Poisson approach.
All statistical tests were 2-sided. Analyses were performed with SAS software version 6.12 (SAS Institute, Cary, North Carolina) and S-Plus version 3.4 (Insightful, Seattle, Washington).

**Results**

**Baseline Characteristics**

Of the 213 patients with IgM MGUS, 123 (58%) were male and 90 (42%) were female. The median age at diagnosis was 74 years (range, 24-94 years). Only 3 patients (1%) were younger than 40 years, and 64% were 70 years or older. Thirty-five percent of patients had a history of cancer in first-degree relatives, and 24% had a personal history of malignancy. Skin cancer accounted for 27%, 18% gave a history of genitourinary cancer, and 16% had a history of breast cancer.

The value for the serum M protein at diagnosis ranged from unmeasurable (visible as a small band on electrophoresis but not quantifiable by densitometry) to 2.6 g/dL (median, 1.2 g/dL) (Fig. 1). Only 53% of the patients had an M-protein value more than 1.0 g/dL at diagnosis. The IgM gammopathy was associated with a small non-IgM gammopathy (biclonal) in 3 patients (1%). In 1 patient, the non-IgM component disappeared during follow-up. The light chain was κ in 70% and λ in 30%. The mobility of the M spike was γ in 85.5%, β-γ in 10%, β in 4%, and α2-globulin in 0.5%. The quantitative IgM value ranged from 40 to 4,800 mg/dL (median, 675 mg/dL). Fifteen percent of patients had a normal nephelometric IgM value of 300 mg/dL or less. The concentration of uninvolved (normal, polyclonal, or background) immunoglobulins was reduced in 35% of 129 patients whose immunoglobulin concentration was determined quantitatively. Electrophoresis, immunoelectrophoresis, and
immunofixation were performed on urine from 64 of the patients with IgM MGUS (19% had a monoclonal κ light chain, 8% had a λ light chain, and 73% were negative for a monoclonal light chain). Only 3 patients had more than 100 mg of light chain per 24 hours.

The initial hemoglobin value ranged from 5.9 to 18.9 g/dL (median, 14.0 g/dL) (Table 1). Only 17% of patients had a hemoglobin value less than 12.0 g/dL, and in 4% it was less than 10 g/dL. However, the anemia was due to causes other than the monoclonal gammopathy (eg, myelodysplasia, renal insufficiency, iron deficiency). Only 1% had a platelet count less than 100 x 10^9/L, and 3% had a platelet level more than 500 x 10^9/L. The sedimentation rate was less than 30 mm in 1 hour in 51% and more than 100 mm in 1 hour in only 7%. The serum albumin value ranged from 1.9 to 4.5 g/dL (median, 3.4 g/dL), but only 14% had an albumin value less than 3 g/dL. The serum creatinine value was 2.0 mg/dL or more in 7%, but this was not related to the monoclonal gammopathy in any instance. Of 126 patients in whom cryoglobulins were sought, 8 (6%) had positive results. Serum viscosity, determined in only 9 patients, ranged from 1.5 to 3.2 cP (median, 1.9 cP).

Bone marrow examination was done in 27 patients: 24 had normal or nondiagnostic results, 2 had an inadequate specimen, and 1 had disseminated vasculitis. All had less than 10% plasma cells in the bone marrow aspirate. Patients who were asymptomatic and had no hepatosplenomegaly or lymphadenopathy, no constitutional symptoms, and no anemia were not subjected to a bone marrow examination, in accordance with our clinical practice.
The liver was palpable in 10% of patients and ranged in size from 1 to 11 cm (median, 2.5 cm) below the right costal margin. The spleen was palpable in only 5 patients: 1 cm below the left costal margin in 4 and 6 cm below the costal margin in 1.

**Outcomes**

The 213 patients were followed for 1,567 person-years (median, 6.3 years; range, 0-20.6 years), during which 152 (71%) died. During follow-up, non-Hodgkin lymphoma, Waldenström macroglobulinemia, primary amyloidosis, and chronic lymphocytic leukemia occurred in 29 patients (14%) (Table 2). The rate of progression did not increase soon after recognition of the IgM MGUS but gradually increased throughout the period of observation. This strongly suggests that patients with early or smoldering macroglobulinemia were not included in our IgM MGUS cohort. The non-Hodgkin lymphomas were classified as lymphoplasmacytic (6 patients), diffuse large B-cell (5), mucosa-associated lymphoid tissue (MALT) (2), small lymphocytic (1), follicular (1), large cell (presumably B-cell) (1), and B-cell unclassified (1). The cumulative probability of progression to one of these disorders was 10% at 5 years, 18% at 10 years, and 24% at 15 years (Fig. 2). The overall average risk of progression was about 1.5% per year. Patients were at risk for progression even after having stable MGUS for 20 years or more. Of the 17 patients in whom lymphoma developed, 3 had this progression after 5 years of observation. Of the 6 patients in whom Waldenström macroglobulinemia developed, 5 had this progression more than 5 years after recognition of the M protein. In 2 additional patients, an M-protein value more than 3 g/dL developed, but no therapy was required. One other patient had an IgM λ monoclonal gammopathy (982 mg/dL), but a
biclonal gammopathy (IgM 386 mg/dL + IgA κ 2,840 mg/dL) developed 5 years later. The bone marrow contained more than 15% plasma cells, and the patient was thought to have a smoldering multiple myeloma that did not necessitate immediate therapy.

The rates of death due to other disease, which included cardiovascular and cerebrovascular diseases and cancers that were not of lymphoid or plasmacytic origin, were 31% at 5 years, 52% at 10 years, and 65% at 15 years. In comparison, in a competitive model, the rates of progression due to lymphoplasma cell cancers were 8% at 5 years, 12% at 10 years, and 15% at 15 years (Fig. 3). Patients with IgM MGUS had a shorter median survival than expected for Minnesota residents of matched age and sex (7.0 vs 10.8 years, \( P < .001 \)) (Fig. 4).

The number of patients with progression to a lymphoid neoplasm or related disorder (29 patients) was 15.9 times that expected on the basis of incidence rates for those conditions in the general population (Table 2). The risk of disease was increased by a factor of 14.8 for non-Hodgkin lymphoma, 262 for macroglobulinemia, 16.3 for primary amyloidosis, and 5.7 for chronic lymphocytic leukemia.

The M protein disappeared in 9 patients during follow-up. All of these patients had a low initial concentration of M protein; only 1 had a value more than 1.0 g/dL (1.2 g/dL) at diagnosis.

**Risk Factors for Progression**

The baseline factors evaluated in a univariate model included age; sex; presence of hepatosplenomegaly; values for hemoglobin, serum calcium, alkaline phosphatase, creatinine, and albumin; concentration of serum M protein; presence, type, and amount of monoclonal urinary light
chain; reduction in uninvolved immunoglobulins; platelet value; prothrombin time; and sedimentation rate (Table 3). The values for hemoglobin and serum albumin and the sedimentation rate were significant, whereas the serum M-protein value was of borderline significance ($P=0.06$). Factors, including splenomegaly, platelet value, prothrombin time, sedimentation rate, reduction of uninvolved immunoglobulins, and size of urine M protein, in which more than 10% of the values were missing, were excluded from multivariate analysis. Only the concentration of the serum M protein ($P=0.03$) at diagnosis and the serum albumin value ($P=0.01$) were independent predictors of progression with multivariate analysis. A reduction in one or more uninvolved immunoglobulins and the presence of a monoclonal light chain in the urine were not risk factors for progression (Fig. 5).

The relative risk of progression was directly related to the concentration of the M protein in the serum at the time of diagnosis of MGUS. The risk of progression to lymphoma or a related malignancy 10 years after recognition of MGUS was 14% for an initial M-protein value of 0.5 g/dL or less, 26% for 1.5 g/dL or less, and 41% for 2.5 g/dL (Fig. 6). The risk of progression to lymphoma or a related disorder at 10 years with an initial M-protein value of 1.5 g/dL was 1.8 times the risk of progression with an initial value of 0.5 g/dL or less; the risk of progression with an M-protein value of 2.0 g/dL was 2.8 times the risk of progression with an initial value of 0.5 g/dL or less; and the risk of progression with an M-protein value of 2.5 g/dL was 3.1 times the risk of progression with an initial value of 0.5 g/dL or less.
Discussion

Patients with MGUS are at increased risk for progression to multiple myeloma, lymphoma, Waldenström macroglobulinemia, primary amyloidosis (AL), or a related plasma cell disorder. In patients with IgG or IgA MGUS, the risk of development of multiple myeloma and related disorders is well characterized and recently was the subject of 2 large studies. Although patients with IgM MGUS were included in these 2 studies, there was no specific analysis of progression in patients with IgM MGUS. A detailed and specific study of IgM MGUS is needed because the rate and nature of progression differ from those of IgG or IgA MGUS. IgG and IgA MGUS arise from mature, somatically mutated, postswitch plasma cells, and approximately 50% have evidence of translocations in the immunoglobulin heavy-chain region, 14q32. In contrast, IgM MGUS arises from somatically mutated postgerminal center B lymphocytes that have not undergone isotype class switching. Thus, translocations of 14q32 are not found in IgM MGUS (Fonseca R, personal communication, December 2002). As a result, the phenotype of progression in IgM MGUS is completely different from that in IgG or IgA MGUS. In essence, IgM MGUS can be considered a distinct biological and clinical entity, whose only relationship to IgA and IgG MGUS is the presence of secreted monotypic immunoglobulin.

Among older studies of MGUS reported so far, only a few series of rather modest size and with suboptimal duration of follow-up have studied IgM monoclonal gammopathies. Patients with IgM MGUS constituted only a small proportion of patients in these studies. In 1 study, IgM monoclonal gammopathy was an incidental finding in 31% of 160
asymptomatic patients, but only 11 were classified as having benign disease (MGUS) after follow-up. In the majority of these patients, Waldenström macroglobulinemia or a malignant lymphoma developed, and the authors emphasized the need for follow-up of more than 10 years. In another study,11 13 of 34 patients had a benign IgM monoclonal gammopathy, but most patients were followed for only 1 to 3 years. In another series, 3 of 28 patients with an IgM gammopathy appeared to have benign disease, but 4 others had unrelated conditions.12 Waldenström13 reported that 44 of 67 patients with an IgM gammopathy remained stable without treatment for a “long time.” In another report, 26 of 263 patients had MGUS of the IgM class. Macroglobulinemia (4 patients), lymphoma (3), and chronic lymphocytic leukemia (1) developed during a follow-up of 5 to 20 years. Macroglobulinemia was diagnosed at a median of 6 years after recognition of the MGUS, whereas MGUS had been present for 6, 13, and 15 years in 3 patients in whom a malignant lymphoma developed.25 Duration and results of follow-up were not given in a series of 106 patients with an IgM paraprotein, of whom 22 had IgM MGUS.26 In a report of 242 patients with MGUS of the IgM type diagnosed at Mayo Clinic from 1956-1978,9 40 (17%) had development of a malignant lymphoid disorder. This occurred an average of 4 years after recognition of the M protein. The majority of patients with progression had Waldenström macroglobulinemia or lymphoma.

MGUS of the IgM type has been included in large series of MGUS, but there has been no effort for separate analysis of patients with MGUS of the IgM type. In the Gregersen series from Jutland,14 246 of the 1,324 patients with MGUS had the IgM type, but their follow-up data were
not separated from those with IgG or IgA proteins. Of our 1,384 patients with MGUS, 214 had the IgM type, but detailed laboratory features and prognosis were evaluated for the entire group, although there was initial evidence that the rate of progression in IgM MGUS was higher than that in IgG or IgA MGUS.\(^8\) Cesana et al.\(^{15}\) reported that 130 of 1,104 patients with MGUS had the IgM type, but, again, features of IgM monoclonal gammopathy were not examined separately. Therefore, our current knowledge is limited by the small number of patients and the modest follow-up in most series and by the fact that data on IgM MGUS were combined with data on IgG and IgA MGUS in the larger studies.

This article describes 213 patients with IgM MGUS who were followed for 1,567 person-years. The relative risk of progression to lymphoma was 14.8-fold, and the risk for Waldenström macroglobulinemia was increased 262-fold in the IgM MGUS group. In contrast, the risk of progression to lymphoma was not increased in the cohort of 1,170 non-IgM patients from southeastern Minnesota. Furthermore, multiple myeloma was increased 30-fold in the non-IgM patients. In the 1,170 non-IgM patients, median age was 72 years, the percentage older than 70 years was 54\%, and the percentage younger than 40 years was 2\%; the respective values in the 213 patients with IgM MGUS were 74 years, 64\%, and 1.8\%. Males constituted 54\% of the non-IgM cohort and 58\% of the IgM MGUS patients. The size of the M protein in both cohorts was the same (1.2 g/dL). A serum monoclonal κ light chain was found in 21\% and a λ light chain in 10\% of the non-IgM cohort; in the IgM MGUS group, these percentages were 19\% and 8\%.
Importantly, the study is population-based, because all patients came from a defined geographic area (southeastern Minnesota) in which referral occurs almost exclusively to Mayo Clinic in Rochester. We defined MGUS of the IgM type by the presence of an IgM M protein with a concentration of 3 g/dL or less and only modest amounts of monoclonal light chain in the urine and the absence of lymphadenopathy, hepatosplenomegaly, lytic bone lesions, anemia, hypercalcemia, or renal insufficiency related to the M protein. If bone marrow was examined, the marrow had to contain less than 10% plasma cells. Ideally, with unlimited resources and the consent of the patient, bone marrow examination would be of interest in all patients with MGUS of IgM type, as well as in those with IgG and IgA types. We do not believe that a patient’s medical care is compromised by delaying a bone marrow examination until the M-protein value increases or constitutional symptoms, hepatosplenomegaly, lymphadenopathy, or anemia develops. There is universal agreement that patients with IgM MGUS or smoldering (asymptomatic) macroglobulinemia should not be treated (Kyle RA, Therneau TM, Rajkumar SV, et al, read at the 2nd International Workshop on Waldenström’s Macroglobulinemia, Athens, Greece, September 2002.)

The study demonstrates that the risk of development of lymphoma, Waldenström macroglobulinemia, or a related condition occurred at a rate of 1.5% per year throughout follow-up. This rate of progression is higher than the 1% we have reported earlier when all forms of MGUS were considered together, and it is an important finding. Overall, non-Hodgkin lymphoma developed in 17 patients, Waldenström macroglobulinemia in 6, and primary amyloidosis and chronic lymphocytic
leukemia in 3 each. The relative risk for development of one of these related malignant lymphoid diseases was 15.9-fold greater than expected on the basis of incidence rates in the Iowa Surveillance, Epidemiology, and End Results Program.22 The risk of development of non-Hodgkin lymphoma (14.8) is an underestimate because only lymphomas associated with an IgM protein were included as observed cases, whereas the incidence rates for all lymphomas were used to calculate the number of expected cases. As expected, the risk of progression was highest for Waldenström macroglobulinemia. In contrast, distinguishing the patient with a stable monoclonal gammopathy from one in whom lymphoma, Waldenström macroglobulinemia, or a related disorder will eventually develop is difficult when the MGUS is initially recognized. In fact, in the past, if an M protein in a patient with MGUS remained stable for 3 to 5 years, the process was believed to be benign. However, as with other forms of MGUS, this study clearly demonstrates that the risk of progression persists even after 20 years of follow-up. On multivariate analysis, only the initial concentration of the serum M protein and the serum albumin level at diagnosis were independent predictors of progression.

In a comparison of patients with various M-protein values in which 0.5 g/dL or less was used as a reference value, we found that the initial concentration of M protein was a statistically significant predictor of progression. Patients with an IgM protein value of 2.5 g/dL had a 3.1-fold greater risk of progression than patients with a value of 0.5 g/dL. These results are similar to those in our earlier study of 1,384 patients with all forms of MGUS.8 The adverse prognostic effect of the concentration of the M protein is likely a reflection of the impact of a higher tumor burden on
progression. For instance, with a higher tumor burden, more cells are at risk for developing critical genetic changes necessary for progression.

A low serum albumin level was also an important independent indicator of progression. The prognostic value of serum albumin levels has not been described previously, and the possible mechanism for this effect is unclear. Although there was a reduction of uninvolved immunoglobulins in more than a third of patients, this was not indicative of progression, a finding similar to that in other forms of MGUS. The presence of a monoclonal light chain in the urine was also not a risk factor for development of lymphoma or a related disorder. Future studies need to use cytogenetic analysis, high-throughput gene expression arrays, and other molecular studies to identify other, more specific risk factors for progression. However, these studies are difficult to perform in this patient population because routine baseline and follow-up bone marrow biopsies generally are not indicated for clinical purposes.

Lymphoma or a related disorder probably would have developed in the 3 patients who had a significant increase in their gammopathy. However, it is important to keep in mind that patients with IgM MGUS are far more likely to die of an unrelated disease than to have progression to a malignant lymphoid disorder, as shown on this study. The actual risk of death from lymphoma and related disorders is overstated when one ignores the greater risk of death from other causes such as cardiovascular and cerebrovascular diseases or nonlymphoid malignancies in these older patients.
References


Table 1.—Laboratory Values in 213 Patients With IgM Monoclonal Gammopathy of Undetermined Significance*

<table>
<thead>
<tr>
<th></th>
<th>Median</th>
<th>Range</th>
<th>Other</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hemoglobin, g/dL</td>
<td>14</td>
<td>5.9-18.9</td>
<td>&lt;12</td>
</tr>
<tr>
<td>Platelets, x 10^9/L</td>
<td>275</td>
<td>78-783</td>
<td>&lt;100</td>
</tr>
<tr>
<td>Sedimentation rate, in 1 h</td>
<td>29</td>
<td>0-135</td>
<td>≥30</td>
</tr>
<tr>
<td>Creatinine, mg/dL</td>
<td>1.1</td>
<td>0.5-5.4</td>
<td>≥2</td>
</tr>
<tr>
<td>Serum monoclonal protein, g/dL</td>
<td>1.2</td>
<td>0.3-2.6</td>
<td>≥2</td>
</tr>
<tr>
<td>Urine monoclonal protein, g/24 h</td>
<td>0.05</td>
<td>0.01-0.54</td>
<td>&gt;100</td>
</tr>
<tr>
<td>Serum albumin, g/dL</td>
<td>3.4</td>
<td>1.9-4.5</td>
<td>&lt;3</td>
</tr>
</tbody>
</table>

*Condition was diagnosed between 1960 and 1994 in patients in southeastern Minnesota.
Table 2.—Observed and Expected Progression and Standardized Incidence Rates Among 213 Patients With IgM Monoclonal Gammopathy of Undetermined Significance*

<table>
<thead>
<tr>
<th>Disease progression</th>
<th>Observed</th>
<th>Expected†</th>
<th>SIR</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Non-Hodgkin lymphoma</td>
<td>17</td>
<td>1.1</td>
<td>14.8</td>
<td>8.6-23.7</td>
</tr>
<tr>
<td>Amyloidosis</td>
<td>3</td>
<td>0.18</td>
<td>16.3</td>
<td>3.4-47.5</td>
</tr>
<tr>
<td>Macroglobulinemia</td>
<td>6</td>
<td>0.02</td>
<td>262</td>
<td>96.0-569.5</td>
</tr>
<tr>
<td>Chronic lymphocytic leukemia</td>
<td>3</td>
<td>0.53</td>
<td>5.7</td>
<td>1.2-16.5</td>
</tr>
<tr>
<td>Total</td>
<td>29</td>
<td>1.83</td>
<td>15.9</td>
<td>11.0-22.8</td>
</tr>
</tbody>
</table>

SIR, standardized incidence rate.

*Condition was diagnosed between 1960 and 1994 in patients in southeastern Minnesota.

†Iowa SEER Registry.
Table 3.—Risk Factors for Progression in 213 Patients With IgM Monoclonal Gammopathy of Undetermined Significance*

<table>
<thead>
<tr>
<th>Factor</th>
<th>Univariate analysis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>0.43</td>
</tr>
<tr>
<td>Sex</td>
<td>0.96</td>
</tr>
<tr>
<td>Hepatomegaly</td>
<td>0.56</td>
</tr>
<tr>
<td>Hemoglobin value</td>
<td>0.002</td>
</tr>
<tr>
<td>Creatinine value</td>
<td>0.70</td>
</tr>
<tr>
<td>Serum albumin value</td>
<td>0.03</td>
</tr>
<tr>
<td>Serum monoclonal protein concentration</td>
<td>0.06</td>
</tr>
<tr>
<td>Serum monoclonal M-κ or M-λ</td>
<td>0.49</td>
</tr>
<tr>
<td>Urinary monoclonal protein</td>
<td></td>
</tr>
<tr>
<td>Presence</td>
<td>0.28</td>
</tr>
<tr>
<td>Type κ or λ</td>
<td>0.43</td>
</tr>
<tr>
<td>Reduction of uninvolved immunoglobulins</td>
<td>0.73</td>
</tr>
<tr>
<td>Serum alkaline phosphatase value (log)</td>
<td>0.55</td>
</tr>
<tr>
<td>Platelet value</td>
<td>0.90</td>
</tr>
<tr>
<td>Sedimentation rate</td>
<td>0.004</td>
</tr>
</tbody>
</table>

*Condition was diagnosed between 1960 and 1994 in patients in southeastern Minnesota.
Legends

Fig. 1. **Initial monoclonal (M) protein values in 213 patients.** Patients were residents of southeastern Minnesota in whom monoclonal gammopathy of undetermined significance of IgM class was diagnosed from 1960 through 1994.

Fig. 2. **Probability of progression in 213 patients.** Patients were residents of southeastern Minnesota in whom monoclonal gammopathy of undetermined significance (MGUS) of IgM class was diagnosed from 1960 through 1994. Curve shows probability of progression of MGUS to lymphoma, Waldenström macroglobulinemia, primary amyloidosis, or chronic lymphocytic leukemia. The bars show 95% confidence intervals. Numbers at bottom of horizontal axis are numbers of patients at risk at each interval. BMPC, bone marrow plasma cells.

Fig. 3. **Competitive model in 213 patients.** Patients were residents of southeastern Minnesota in whom monoclonal gammopathy of undetermined significance (MGUS) of IgM class was diagnosed from 1960 through 1994. Upper curve shows probability of dying from nonlymphoid diseases. Lower curve shows probability of progression to lymphoma or a related disorder.

Fig. 4. **Survival curves.** Lower curve shows median survival of 213 patients with monoclonal gammopathy of undetermined significance (MGUS) of IgM class. Upper curve shows expected survival of Minnesota residents of matched age and sex.

Fig. 5. **Risk of progression in 213 patients.** Patients were residents of southeastern Minnesota in whom monoclonal gammopathy of undetermined significance (MGUS) of IgM class was diagnosed from 1960
through 1994. Risk is shown with and without reduction of uninvolved immunoglobulins. Numbers at bottom of horizontal axis are numbers of patients at risk at each interval.

Fig. 6. **Relative risk of disease progression in 213 patients.** Patients were residents of southeastern Minnesota in whom monoclonal gammopathy of undetermined significance (MGUS) of IgM class was diagnosed from 1960 through 1994. Risk is by monoclonal protein value at diagnosis.
Figure 2

Cumulative probability, %

- Progression + M protein >3 g/dL
- Progression

Years from diagnosis of MGUS

0 5 10 15 20

213 127 58 23 3

10% 12% 19% 18% 24% 26%
Figure 3

- Progression
- Death from non-lymphoid diseases

Cumulative incidence, %

Years from diagnosis of MGUS
Figure 4

- Observed
- Expected

Median = 10.8 years

Median = 7.0 years

P < .001

Percentage of patients vs. Years from diagnosis of MGUS
Figure 5

Cumulative incidence, %

- No reduction
- 1 or 2 reductions

Years from diagnosis of MGUS

P = .73
Figure 6

Risk of full progression at 10 years

Serum M protein, g/dL

≤0.5 1.0 1.5 2.0 2.5

14 13 26 34 41

5% 14.1% 25% 50% 75%
Long-term follow-up of IgM monoclonal gammopathy of undetermined significance