

Monoclonal Gammopathy of Undetermined Significance: Predictors of Malignant Transformation and Recognition of an Evolving Type Characterized by a Progressive Increase in M Protein Size

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OBJECTIVE: To investigate the predictors of monoclonal gammopathy of undetermined significance (MGUS) by considering not only the initial features but also the pattern of evolution of the M protein during the first years after diagnosis.

PATIENTS AND METHODS: This study consisted of 359 patients diagnosed as having MGUS at a single institution. Patients who showed a definite and progressive increase in their M protein size according to serum electrophoresis during the first 3 years of follow-up were considered to have evolving MGUS, whereas all others were considered to have nonevolving MGUS.

RESULTS: Of the 359 patients, 330 had nonevolving MGUS, whereas 29 fulfilled the criteria for evolving MGUS. Overall, 32 patients developed malignant transformation. The progression rates at 10 and 20 years of follow-up for the evolving and the nonevolving types were 55% vs 10% and 80% vs 13%, respectively. Multivariate analysis revealed that the features significantly associated with a higher risk of progression were evolving MGUS (relative risk [RR], 12.14; $P < .001$), IgA MGUS (RR, 2.93; $P = .006$), and M protein concentration (RR, 2.18; $P = .04$).

CONCLUSION: The evolutionary pattern of serum M protein (progressive increasing vs stable) during the first years of follow-up is the most important risk factor for disease progression in patients with MGUS.

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BMPC = bone marrow plasma cell; MGUS = monoclonal gammopathy of undetermined significance; RR = relative risk; SMM = smoldering multiple myeloma

The term *monoclonal gammopathy of undetermined significance* (MGUS) denotes the presence of a serum monoclonal protein (M protein) in the absence of clinical manifestations attributable to monoclonal gammopathy (eg, multiple myeloma, Waldenström macroglobulinemia, primary amyloidosis, or other related disorders). Several articles have been published during the past 4 decades on the prevalence and incidence of MGUS, showing differences related to populations studied, methods, and study design.¹ In a recent survey, the prevalence of MGUS was 3.2% and 5.7% in persons older than 50 and 70 years, respectively.² To determine whether the prevalence of MGUS will remain stable or evolve into a symptomatic monoclonal gammopathy that requires therapy is a crucial issue. Several studies have shown that a significant proportion of patients develop a symptomatic monoclonal gammopathy, usually after a long period of stability.³⁻⁸

However, one concern in this type of analysis is reproducibility because the results may be biased by the number of patients, the extent of follow-up, or selective referral. On the other hand, in previous studies, only the presenting features have been considered, whereas the evolving pattern during the first years after the recognition of the M protein has not been taken into account. The aim of the current study was to investigate the predictors of outcome considering both the initial features and the evolutionary pattern of the M protein during the first 3 years of follow-up.

PATIENTS AND METHODS

From January 1, 1970, through December 31, 2001, 537 patients were diagnosed as having MGUS at our institution.¹ Of these patients, 359 with a minimum follow-up of 3 years and serial M protein measurements were included in the study. Of the 178 patients excluded, 18 were lost to follow-up, and 160 had a follow-up of less than 3 years. Patients whose disease had evolved into a symptomatic monoclonal gammopathy within the first 3 years after diagnosis were excluded. Patients with smoldering multiple myeloma (SMM)⁹ were also excluded.

LABORATORY AND CLINICAL STUDIES

The type of M protein was determined by immunoelectrophoresis from 1970 to 1993 and by immunofixation since 1993. The M protein quantitation was performed by electrophoresis and the urine M protein detection by cellulose acetate electrophoresis on 50-fold concentrated urine. Bone marrow aspirates obtained at diagnosis were

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TABLE 1. Patient Characteristics at Diagnosis of MGUS According to MGUS Type*

Characteristics	Overall (N=359)	Nonevolving (n=330)	Evolving (n=29)
Age (y) (range)	66 (25-87)	65 (25-87)	68 (37-82)
Hemoglobin level (g/L)	13.4 (6.1-18.5)	13.5 (6.1-18.5)	13 (9.7-15.6)
Creatinine level (mg/dL)	0.9 (0.4-9.9)	0.9 (0.4-9.9)	0.9 (0.7-1.7)
Serum calcium level (mg/dL)	9.5 (8-11.1)	9.6 (8-11.1)	9.5 (8.7-10.5)
Albumin level (g/L)	43 (27-59)	43 (27-59)	43 (34-49)
β_2 -Microglobulin level (mg/dL)	1.9 (1-22.3)	1.9 (1-22.3)	2.1 (1.3-10)
Serum M protein level (g/L)	14.9 (3.4-29.6)	14.8 (3.4-29.6)	14.9 (6.7-24.9)
BMPC count (%)	4 (0-25)	4 (0-16)	6.5 (1-25)
M protein type, No. (%)			
IgG	235 (65)	222 (67)	13 (45)
IgA	68 (19)	59 (18)	9 (31)
Light chain	3 (0.8)	3 (0.9)	0 (0)
κ	204 (57)	186 (56)	18 (62)
λ	152 (42)	141 (43)	11 (38)
Biclonal	1 (0.3)	1 (0.3)	0 (0)
IgM	47 (13)	40 (12)	7 (24)
Biclonal	4 (1)	4 (1)	0 (0)

*Values are median (range) unless indicated otherwise. BMPC = bone marrow plasma cell; MGUS = monoclonal gammopathy of undetermined significance.

reviewed independently by 2 of the examiners (L.R., M.R.) in 228 patients from whom bone marrow samples were available and well preserved. Plasma cell percentages were estimated from a 500-cell count by each examiner, and the mean values were considered. In each patient, the following data were recorded: age, sex, hemoglobin level, white blood cell count, platelet count, serum albumin level, serum creatinine level, serum calcium level, size of the serum M protein, presence of monoclonal urine protein, and percentage of bone marrow plasma cells (BMPCs). Patients were followed up on a yearly basis with an M protein measurement on electrophoresis at each visit.

DEFINITION OF THE EVOLVING AND THE NONEVOLVING TYPES

Only patients with at least 3 years of follow-up in the MGUS status and with sufficient M protein determinations were classified as having evolving or nonevolving MGUS. All 359 study patients who fulfilled these criteria had at least 1 annual measurement of their M protein levels by serum electrophoresis. Two of the authors (L.R., M.T.C.) reviewed all the electrophoresis results. Cases in which the 2 reviewers did not agree on the results were reviewed by a third observer (J.B.). The variable size of the M protein in MGUS (<5 g/L to approximately 30 g/L) and the fact that the M spike is seen in the background of normal immunoglobulins make it difficult to establish a certain measurement value in terms of percentage or threshold. For this reason, the evolving type was defined only as a progressive increase in the M protein size on electrophoresis in each of the annual consecutive measurements during a

period of 3 years (ie, any annual increase in the serial M protein measurements through baseline plus years 1, 2, and 3 needed to be higher compared with each previous one). All patients with unchanged M protein size were considered to have the nonevolving type.

STATISTICAL ANALYSES

The cumulative risk of malignant transformation was calculated according to the Kaplan-Meier method,¹⁰ and different curves were statistically compared by the log-rank test.¹¹ Subsequently, relationships between predictors of transformation were determined by the Cox proportional hazard model for covariate analysis for censored data using SPSS statistical software (StatSoft Inc, Tulsa, Okla).¹² Only easily available data, including age, sex, hemoglobin concentration, white blood cell count, platelet count, size of M protein, serum albumin level, serum creatinine level, immunoglobulin type, light chain type, and proportion of BMPCs, were evaluated for prognostic significance.

RESULTS

The study included 160 men and 199 women, with a median age of 66 years (range, 25-87 years). The main characteristics of patients at diagnosis of MGUS are given in Table 1. Eleven patients had a hemoglobin level lower than 10 g/dL, 11 patients had a serum creatinine level higher than 2 mg/dL, and 7 patients had a serum calcium level higher than 10.5 mg/dL. In all these patients, laboratory abnormalities were not attributable to the monoclonal gammopathy. The median M protein level and

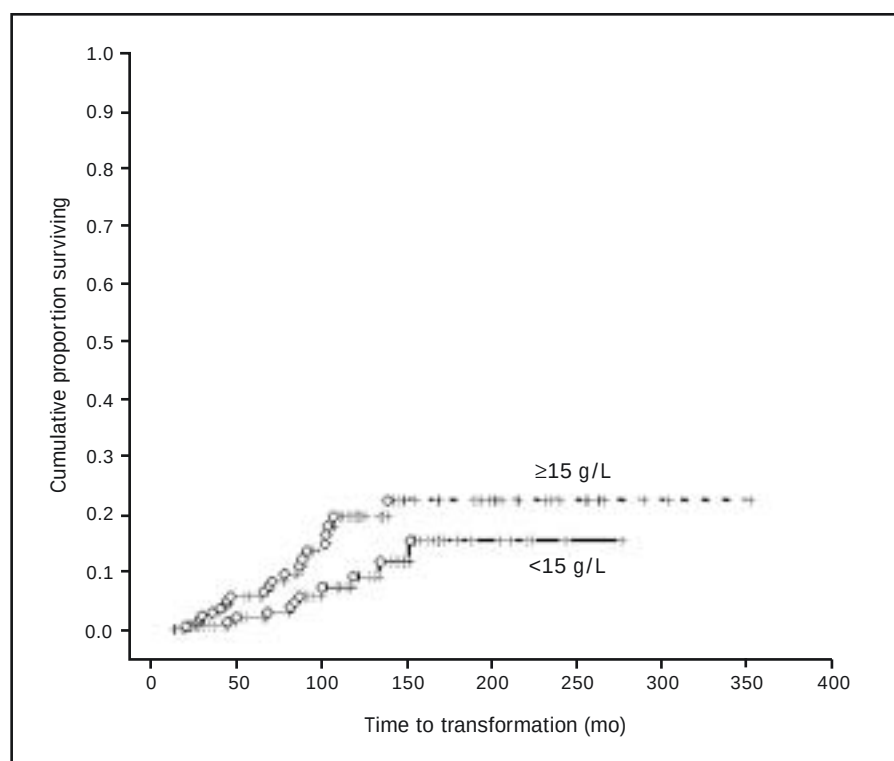


FIGURE 1. Time to transformation and cumulative proportion of patients surviving according to the M serum protein size.

the percentage of BMPCs were 14.8 g/L and 4%, respectively. The 2 examiners highly agreed on their estimation in the percentage of BMPCs, with a major discrepancy being observed in only 7 patients, in whom the BMPC involvement was reassessed by the 2 examiners. Of the 359 patients, 330 had nonevolving MGUS, 29 (8%) of whom fulfilled the diagnostic criteria for evolving MGUS as previously defined. As indicated in Table 1, no significant differences were found at diagnosis between the evolving and the nonevolving types, except for the IgG type, which was more frequent in nonevolving MGUS compared with the evolving variant (67% vs 45%; $P=.005$), and for the IgA plus IgM type, which was more frequent in the evolving subset (55% vs 30%; $P=.04$).

Overall, 32 patients developed malignant transformation (30 had multiple myeloma and 2 had Waldenström macroglobulinemia) after a median follow-up of 93 months. Fourteen (48%) of the 29 patients with evolving MGUS developed symptomatic disease, whereas only 18 (5%) of the 330 patients with nonevolving MGUS had disease that progressed to a malignant condition. The transformation rates at 10 and 20 years of follow-up for the evolving and nonevolving types were 55% vs 10% and

80% vs 13%, respectively. None of the 42 patients in the nonevolving group developed a malignant condition after the first 12 years of follow-up.

In univariate analysis, the initial factors significantly associated with malignant transformation were the serum M protein size, with the highest rate seen when the size was larger than 15 g/L (Figure 1; $P<.001$); the proportion of BMPCs, with the greatest risk seen when the count was higher than 5% (Figure 2; $P=.05$); immunoglobulin isotype, with the higher incidence seen for IgA compared with IgG (Figure 3; $P=.005$); and the type of MGUS (evolving vs nonevolving, Figure 4; $P<.001$).

Multivariate analysis was performed with only the 4 variables that showed a significant predictive value in the univariate analysis (M protein size, percentage of BMPCs, M protein type, and evolving vs nonevolving). In the multivariate analysis, only the M protein size, M protein type, and evolving vs nonevolving type emerged as independent prognostic features (Table 2).

DISCUSSION

Asymptomatic monoclonal gammopathies include MGUS and SMM and are characterized by the presence of a serum

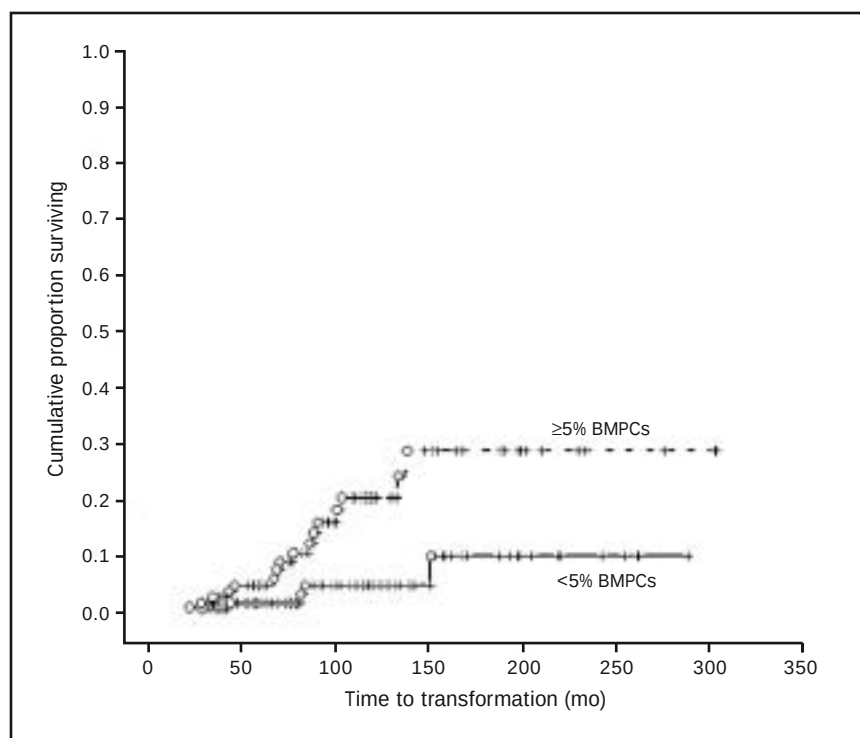


FIGURE 2. Time to transformation and cumulative proportion of patients surviving according to the proportion of the bone marrow plasma cells (BMPCs).

monoclonal protein in the absence of clinical manifestations attributable to the monoclonal gammopathy. MGUS is a common condition, and based on a recent epidemiologic study, its prevalence is even higher than previously recognized.² A significant proportion of patients develop symptomatic monoclonal gammopathy, usually after a long period of stability.^{1,4-8,12} Thus, Kyle et al,⁸ in their most recent update of the seminal Mayo Clinic series, reported an actuarial probability of malignant evolution of 17% at 10 years, 34% at 20 years, and 39% at 25 years, with an annual rate of 1.5%.⁸ In that series, no predictors of malignant evolution were identified. In a smaller series with long follow-up, patients with IgA-type MGUS had a higher probability of malignant evolution.⁴ Baldini et al⁵ highlighted the proportion of BMPCs as an important indicator for MGUS progression. Thus, in patients who fulfilled the MGUS criteria, except for a proportion of BMPCs between 10% and 30% (monoclonal gammopathy of borderline significance), the probability of malignant transformation was significantly higher than with typical MGUS (37% vs 7% after a median follow-up of 53 and 70 months, respectively). In addition, these authors identified a subset of MGUS with a low risk of transformation (ie, <5% of BMPCs and serum M protein level <15 g/L). Cesana et al,⁷ in a series of 1104 patients,

found a cumulative transformation probability of 14% and 30% at 10 and 15 years, respectively. A bone marrow plasmacytosis greater than 5%, presence of light chain proteinuria, polyclonal serum immunoglobulin reduction, and high erythrocyte sedimentation rate were independent factors that influenced MGUS transformation. In the largest series reported so far, which included 1384 patients from southeastern Minnesota, the probability of progression was 12%, 25%, and 30% at 10, 20, and 25 years of follow-up, respectively.⁶ In that series, the initial serum M protein size and the non-IgG type were the most important predictors of progression. In a previous study from our group, the risk of malignant transformation was 15% at 10 years and 34% at 20 years. In that study, the serum M protein concentration (<15 g/L vs ≥15 g/L; relative risk [RR], 2.6), the percentage of BMPCs (<5% vs ≥5%; RR, 2.2), and the light chain type (κ vs λ; RR, 4.1) were the variables associated with a higher risk of progression in the multivariate analysis.¹³ Finally, Rajkumar et al¹⁴ recently reported that patients with non-IgG MGUS, an M protein size larger than 15 g/L, and an abnormal κ/λ light chain ratio had an actuarial probability of malignant evolution of 58% at 20 years of follow-up, whereas for patients with IgG type, an M protein size less than 15 g/L, and a normal κ/λ light chain ratio, the

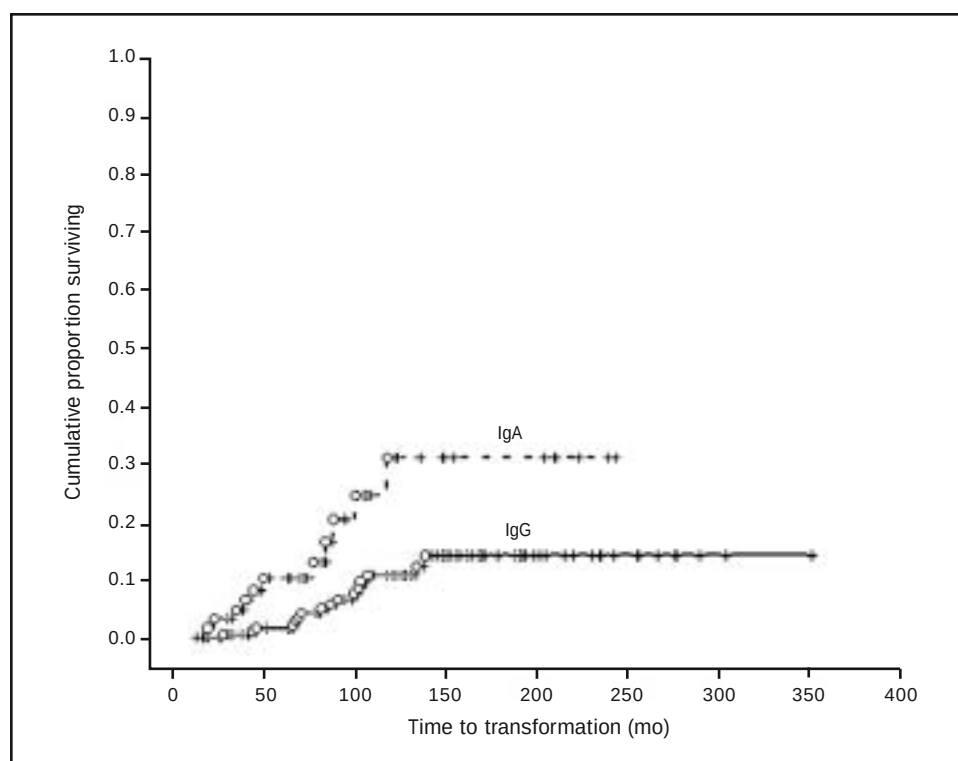


FIGURE 3. Time to transformation and cumulative proportion of patients surviving according to the immunoglobulin type (IgG vs IgA).

probability of malignant evolution at 20 years was only 6%.

On the basis of the previous studies, it seems that the plasma cell burden, measured by the M protein size and/or the extent of BMPC involvement, and IgA type are the critical factors for malignant transformation in MGUS.^{4-7,12} In this regard, the results of our multivariate analysis fully support the impact of plasma cell burden and IgA type on MGUS malignant evolution.

Kyle and Greipp⁹ first described SMM in patients who fulfilled the diagnostic criteria of multiple myeloma (ie, a serum M protein level >30 g/L and a proportion of BMPCs of $\geq 10\%$) but had no organ-related impairment. We recently reported the natural history of 53 patients with SMM diagnosed according to the stringent criteria of Kyle and Greipp, and we described the evolving SMM type.¹⁵ Thus, patients with evolving SMM show a progressive increase in the serum M protein level until symptomatic myeloma develops, whereas patients with nonevolving SMM are characterized by a stable M protein level until the onset of symptomatic disease, with the evolving type having a shorter time to progression compared with the nonevolving type. Interestingly, 59% of patients with the evolving SMM type had a previously recognized MGUS

that also had an evolving pattern, whereas a previous MGUS was observed in only 4% of patients with the nonevolving type. We also found that this different natural history correlates with the different pattern of genetic abnormalities detected by comparative genomic hybridization in both subtypes of SMM.¹⁶ Thus, the comparative genomic hybridization pattern in evolving SMM is similar to the comparative genomic hybridization changes reported in patients with the symptomatic de novo multiple myeloma, with a high frequency of chromosomal losses and 1q gains, whereas chromosomal losses are uncommon in the nonevolving group. Moreover, none of the patients in this group showed 1q gains.

On the basis of our observations in patients with SMM, we hypothesized that there are 2 types of asymptomatic monoclonal gammopathies, evolving and nonevolving, which have different natural histories and probably different pathogenetic mechanisms. We hypothesized that eventually all patients with an evolving SMM have an initial phase of MGUS, also with an evolving pattern, because evolving SMM is a transition phase between MGUS and symptomatic multiple myeloma. Moreover, we hypothesized that nonevolving SMM is comparable to nonevolving MGUS but with a higher probability of progression simply because of

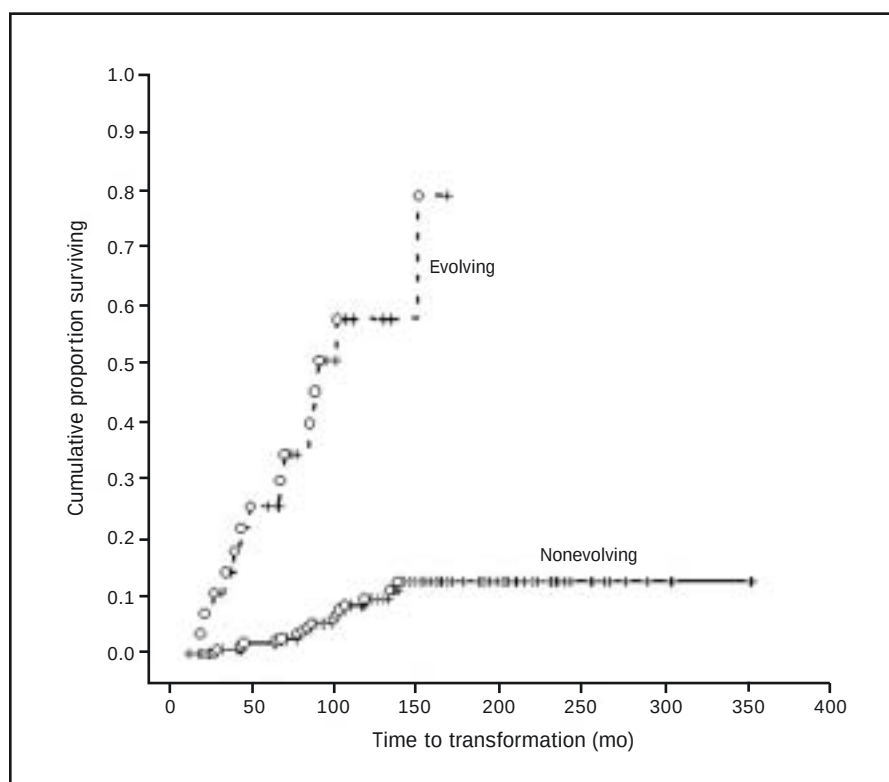


FIGURE 4. Time to transformation and cumulative proportion of patients surviving according to the type of monoclonal gammopathy of undetermined significance (evolving vs nonevolving).

its higher plasma cell mass. In fact, as previously mentioned, the tumor burden measured by the BMPCs and/or the serum M protein level was almost universally found as an adverse prognostic factor for malignant transformation in previously published series.^{5-7,12} In fact, all patients with high tumor mass asymptomatic monoclonal gammopathy (ie, SMM) will eventually develop a symptomatic multiple myeloma, whereas only 25% of patients with MGUS (lower tumor mass than SMM) will ultimately have evolution to a symptomatic monoclonal gammopathy. The clinical outcome of our patients with MGUS also confirms the existence of 2 types of MGUS: an evolving variant, which has a high malignant transformation rate and shorter time to progression, and a nonevolving type, which has a long-lasting stable M protein size and a lower probability of malignant transformation. Our results indicate that all patients with evolving MGUS will eventually develop symptomatic disease. In fact, the actuarial probability of malignant evolution in the evolving type at 20 years is 80%, and at multivariate analysis the evolving pattern emerged as the most important risk factor for malignant transformation, even with a much higher RR than that of tumor burden. Thus, the dynamics of the tumor during the first years of follow-up constitute a key factor for malignant trans-

formation. In this setting, the last part of the curve of actuarial transformation of nonevolving MGUS is also of interest. In this group, which included 42 patients, there were no cases of transformation beyond 12 years of follow-up. This population of patients may have developed protective mechanisms that maintained the tumor clone in an indolent state.

Our hypothesis is that evolving MGUS can be considered an early myeloma with the same pathogenetic mechanisms as multiple myeloma, whereas nonevolving MGUS is a true MGUS, probably needing a second oncogenic event to initiate the malignant transformation. What promotes or limits the growth of these clones is still unknown. New technologies, such as comparative genomic hybridization or gene expression studies, may reveal new

TABLE 2. Multivariate Analysis Results*

Variable	RR (95% CI)	P value
M protein size (>15 g/L)	2.18 (1.02-4.66)	.04
BMPCs ($\geq 5\%$ vs <5%)	1.88 (0.64-5.54)	.25
IgA vs non-IgA	2.93 (1.36-6.29)	.006
Evolving vs nonevolving type	12.14 (5.8-25.4)	<.001

*BMPCs = bone marrow plasma cells; CI = confidence interval; RR = relative risk.

insights into the pathogenetic development of monoclonal gammopathies and can help in the identification of molecular markers that will predict the progression from asymptomatic to clinically overt disease and perhaps lead to development of preventive therapies, particularly for patients at high risk of disease progression (ie, initial high plasma cell mass or evolving type).

CONCLUSION

In previous studies of predictors of malignant evolution in MGUS, only the presenting features were analyzed. In the current study, the pattern of evolution of the serum M protein (progressive increase during the first 3 years of follow-up; evolving MGUS vs stable nonevolving MGUS) emerged as the most important independent predictor of malignant transformation, followed by IgA type and M protein concentration.

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