Changing Pattern of Presentation in Monoclonal Gammopathy of Undetermined Significance

A Single-Center Experience With 1400 Patients

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Abstract: To assess whether the pattern of presentation and the outcome of monoclonal gammopathy of undetermined significance (MGUS) have changed over the last 3 decades, we evaluated 1400 patients, divided into 3 groups: group I (1975–1987), group II (1988–1997), and group III (1998–2007).

We observed a significant increase in age ($p = 0.001$), IgM and biclonal MGUS ($p = 0.003$), hemoglobin ($p < 0.0001$), and albumin ($p = 0.0001$), and a significant reduction of monoclonal (M)-protein concentration ($p < 0.0001$), percentage of bone marrow plasma cells ($p < 0.0001$), and β_2-microglobulin ($p = 0.0001$) over the 3 decades. The proportion of patients with M-protein <1.5 g/dL was significantly higher in group III (66%) than in group II (44%) and group I (26%) ($p < 0.0001$). By Kaplan-Meier analysis, group III had a significantly lower 5-year probability of transformation (5%) compared to group II (12%) and group I (22%) ($p = 0.003$). Patients with M-protein <1.5 g/dL had the same life expectancy as the general population (standardized mortality ratio 1.09; $p = 0.41$).

In conclusion, we found that the pattern of presentation of MGUS has changed over time and now includes a higher proportion of patients with more favorable presenting features and probably a better outcome compared to patients presenting in the past. This changing scenario calls for revising the current concepts of the clinical significance of MGUS and the management of patients.

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Abbreviations: BMPC = bone marrow plasma cells, FLC = free light chains, M = monoclonal, MGUS = monoclonal gammopathy of undetermined significance, SMR = standardized mortality ratio.

INTRODUCTION

Monoclonal gammopathy of undetermined significance (MGUS) is defined by the presence of a serum monoclonal (M)-protein of 3 g/dL or less, 10% or fewer plasma cells in the bone marrow, and absence of lytic bone lesions, hypercalcemia, renal insufficiency or anemia related to the M-protein.[9] The rate of progression of MGUS to multiple myeloma or a related disorder is 1%–2% per year.[2,3,5,13] The main risk factors for progression are the size[2,5,7,11,16] and type[3,5,7,11,16] of serum M-protein, the percentage of bone marrow plasma cells (BMPC)[2,5,16] and an abnormal serum free-light chain (FLC) ratio.[15] The prevalence of MGUS increases with age, reaching 3% among people aged 50 years or older and 5% among those over the age of 70 years.[12] The prevalence of MGUS has increased in recent years due to the prolongation of life expectancy and the advent of more sensitive diagnostic methods able to detect minimal monoclonal bands.[1,12,14,19] Therefore, the occasional finding of small M-proteins has become rather common in regular clinical practice. Most of these small components were missed in the past and therefore are underrepresented in prior studies on the prognostic significance of MGUS. We conducted the current study to evaluate whether MGUS patients diagnosed in recent years have more favorable presenting features and a better outcome compared to patients diagnosed in past decades.

PATIENTS AND METHODS

We retrospectively evaluated 1400 consecutive patients with MGUS, diagnosed at the Division of Hematology, Fondazione IRCCS Policlinico San Matteo, University of Pavia, Italy from January 1975 to December 2007. Patients were referred to our institution mainly by their physicians and less frequently by other hospitals. Of the 1499 consecutive patients identified in the original database, 99 were excluded for the following reasons: the diagnosis of MGUS was not confirmed at subsequent evaluations, and patients were reclassified as having primary amyloidosis or POEMS syndrome; the diagnosis was done in another center and presenting features were not available; the patient was lost to follow-up after the first visit. The study was conducted in accordance with the Helsinki Declaration of 1964, as revised in 2000. Patients were divided into 3 groups according to the date of diagnosis: from 1975 to 1987 (group I), from 1988 to 1997 (group II), and from 1998 to 2007 (group III). The diagnostic criteria proposed by the International Myeloma Working Group[9] were used from 2003 on, and were retrospectively applied to patients diagnosed previously. The type of M-protein was defined by immunoelectrophoresis until 1984 and then by immunofixation. Serum M-protein was quantified using serum protein electrophoresis on cellulose acetate. Urine M-protein was quantified using cellulose acetate electrophoresis. Levels of uninvolved immunoglobulins were evaluated by means of nephelometry. Serum FLC levels were determined using FLC assay in patients diagnosed from 2005 on. Plasma cell percentages were estimated on bone marrow smears from a 500-cell count. The presence of lytic bone lesions was evaluated by means of skeletal X-rays. For each patient, the following data were collected at diagnosis: hemoglobin, white blood cell and platelet count, serum creatinine, serum calcium, β_2-microglobulin, serum albumin, type and size of M-protein,

serum FLC levels, polyclonal serum Ig levels, presence and quantification of urine M-protein, percentage of BMPC, skeletal survey. During follow-up, patients underwent blood counts, serum creatinine, serum calcium, quantification of serum and urine M-protein every 6 months during the first year after diagnosis and once a year thereafter.

Statistical Analysis

Continuous variables were reported as median and range, and categorical variables as absolute and relative frequencies. Differences among groups of patients diagnosed in different decades were evaluated using the chi-square test for categorical variables and Kruskal-Wallis nonparametric ANOVA for numerical variables. Cumulative survival probability and cumulative probability of transformation into multiple myeloma or lymphoproliferative disorder were calculated by means of the Kaplan-Meier estimator and compared with the Gehan-Wilcoxon test. Multivariate Cox proportional hazards regression was used to investigate potential risk factors for disease progression. The incidence of death was calculated for each group of patients. Comparison of mortality in different time periods was performed with the log-likelihood ratio test. Survival of MGUS patients with respect to age and sex-matched general population was evaluated by calculating the standardized mortality ratio (SMR), defined as the ratio of observed-to-expected number of deaths. The expected survival of the general population was obtained from Italian life tables provided by ISTAT (Istituto Nazionale di Statistica). Statistical analyses were performed using Stata SE 9 (StataCorp LP), Statistica 8 (StatSoft Inc.), and Microsoft Excel 2000. A p value of 0.05 was considered statistically significant.

RESULTS

The study was performed on a cohort of 740 male patients (53%) and 660 female patients (47%). The median age of patients was 63 years (range, 20–92 yr); 96 patients (7%) were younger than 40 years, whereas 408 (29%) were aged 70 years or older. The main clinical characteristics of patients at diagnosis are reported in Table 1. The median time from the first detection of M-protein to the diagnostic workup at our institution was 3.2 months (range, 1–264 mo).

The presenting features of patients according to the decade of diagnosis are reported in Table 2. From group I to group III there was a significant increase in median age (p = 0.001), IgM and biclonal MGUS (p = 0.003), and hemoglobin (p < 0.0001) and serum albumin (p = 0.0001) levels, and a significant reduction of serum M-protein concentration (p < 0.0001), BMPC percentage (p < 0.0001), and β_2-microglobulin (p = 0.0001). The proportion of patients with a serum M-protein lower than 1.5 g/dL at diagnosis was significantly higher in group III (66%) compared to group II (44%) and group I (26%) (p < 0.0001) (Table 3).

The median follow-up was 40 months (range, 3–396 mo), corresponding to 7577 person-years. During follow-up, 103 patients (7%) had malignant transformation, 91 to multiple myeloma and 12 to lymphoproliferative disorder. The probability of transformation was 9% at 5 years, 18% at 10 years, 28% at 15 years, and 45% at 20 years (Figure 1). In univariate analysis, factors associated with an increased probability of evolution were the size of serum M-protein (p < 0.0001), hemoglobin (p = 0.04) and the Ig isotype, with higher incidence of transformation in IgA than in IgG or IgM MGUS (p = 0.01). Age, sex, type of light chain, serum albumin, β_2-microglobulin, and detectable Bence-Jones proteinuria were not associated with

TABLE 1. Patient Characteristics at Diagnosis

Variable	No. of Patients Evaluated	Result
Age (yr), median (range)	1400	63 (20–92)
Male/female, no. of pts (%)	1400	740 (53)/660 (47)
Hemoglobin (g/dL), median (range)	1339	14 (8.6–19.7)
Serum calcium (mg/dL), median (range)	867	9.4 (7.7–11)
Serum creatinine (mg/dL), median (range)	1034	0.9 (0.1–1.8)
Serum albumin (g/dL), median (range)	1050	4.3 (2.7–5.4)
β_2-microglobulin (mg/dL), median (range)	842	1932 (865–44,300)
Isotype, no. of pts (%)	1395	
IgG		1024 (73)
IgA		151 (11)
IgM		181 (13)
IgD		1 (0)
Biclonal		38 (3)
Type of light chain, no. of pts (%)	1391	
k /		871 (63)/
λ		508 (36)
Biclonal		12 (1)
Serum free-light chains (mg/L), median (range)	236	
k		17.1 (1.4–423)
λ		17.1 (2–299)
Size of serum M-protein (g/dL), median (range)	1375	1.4 (0.1–3)
Uninvolved immunoglobulins (mg/dL), median (range)	984	
IgG		1350 (110–7460)
IgA		162 (22–2370)
IgM		94 (40–4680)
Detectable urine M-protein, no. of pts (%)	1113	210 (19)
BMPC (%), median (range)	704	5 (1–10)

a higher risk of evolution. In multivariate analysis, the size of serum M-protein (p = 0.005), BMPC percentage (p = 0.048), and hemoglobin levels (p = 0.045) were independent risk factors for malignant transformation. By Kaplan-Meier analysis, group III had a significantly lower 5-year probability of transformation (5%) compared to group II (12%) and group I (22%) (p = 0.003) (Figure 2).

The incidence of death was respectively 3.5 × 100 person-years in group I, 3.0 in group II, and 2.5 in group III. The difference between group I and group III was not statistically significant (log likelihood ratio test, 0.08). The median overall survival of the entire series of MGUS patients was 18.9 years. Compared to the general population, patients with MGUS had a significantly higher mortality, with 221 deaths observed versus 162 expected, (SMR, 1.37; 95% CI, 1.2–1.5; p < 0.0001). The causes of death were as follows: multiple myeloma or lymphoproliferative disorder (51 patients, 23%), unrelated (108 patients, 49%), and unknown (62 patients, 28%). Patients with serum

TABLE 2. Pattern of Presentation by Decade of Diagnosis

	Group I (1975–1987) (n = 102)	Group II (1988–1997) (n = 379)	Group III (1998–2007) (n = 919)	P Value
Age (yr), median (range)	59 (27–79)	63 (20–85)	64 (23–92)	0.001
Sex, no. of pts (%)				
M	50 (49)	185 (49)	505 (55)	NS
F	52 (51)	194 (51)	414 (45)	
Hemoglobin (g/dL)				
Median	13.5	13.7	14.1	<0.0001
Range	8.6–19.7	8.7–17.7	9–19.5	
Serum albumin (g/dL)				
Median	3.9	4.3	4.3	0.0001
Range	3.1–5.2	2.9–5.3	2.9–5.4	
β_2-microglobulin (mg/dL)				
Median	2425	1910	1850	<0.0001
Range	1700–5750	895–7830	865–44,300	
Isotype, no. of pts (%)				
IgG	79 (80)	290 (77)	655 (71)	0.003
IgA	14 (14)	43 (11)	94 (10)	
IgM	6 (6)	41 (11)	134 (15)	
IgD	-	-	1 (<1)	
Biclonal	-	5 (1)	33 (4)	
Type of light chain, no. of pts (%)				
K	65 (66)	236 (62)	570 (62)	NS
λ	33 (34)	142 (37)	333 (36)	
Biclonal	-	1 (<1)	11 (1)	
Size of M-protein (g/dL)				
Median	1.7	1.6	1.3	<0.0001
Range	0.7–3	0.1–3	0.1–3	
Bone marrow plasma cells (%)				
Median	8	7	5	<0.0001
Range	1–10	1–10	1–10	

Abbreviations: NS = not significant.

M-protein levels <1.5 g/dL had the same life expectancy as the general population, with 85 deaths observed compared with 78 expected (SMR, 1.09; 95% CI, 0.88–1.35; p = 0.41).

DISCUSSION

This single-center study includes 1400 patients with MGUS diagnosed and followed at a single institution for a median of 40 months. The main clinical characteristics of patients at presentation are similar to those reported in other series.[2,3,5,13]

In the current study, the median age of patients at diagnosis was 63 years, and 7% of patients were aged younger than 40 years. In the Mayo Clinic series by Kyle et al,[11] the median age at diagnosis was 72 years, and fewer than 2% of patients were aged younger than 40 years. A possible explanation for this finding is selective referral, as younger patients are more frequently sent by their physicians or by other hospitals to a large hematologic center for further investigation.

The rate of progression to multiple myeloma or lymphoproliferative disorder is about 2% per year, in line with previous

TABLE 3. Distribution of Patients by Decade of Diagnosis* and Size of M-Protein†

	M-Protein Size (g/dL)			
	<1 No. (%)	≥1–<1.5 No. (%)	≥1.5–<2 No. (%)	≥2 No. (%)
Group I (n = 100)	4 (4)	22 (22)	39 (39)	35 (35)
Group II (n = 366)	45 (12)	117 (32)	125 (34)	79 (22)
Group III (n = 909)	235 (26)	363 (40)	209 (23)	102 (11)
Total (n = 1375)	284 (21)	502 (36)	373 (27)	216 (16)

*See Table 2 for years included for each group.
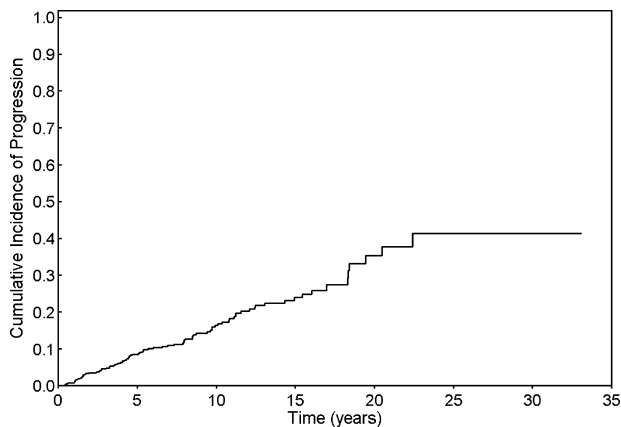†The size of serum M-protein was not reported in 25 patients.

FIGURE 1. Risk of malignant transformation in patients with MGUS.

reports with similar median age[2,3,5] and higher than that observed by Kyle et al,[11] who reported a rate of progression of 1% per year. The younger age of patients included in our study could account for this discrepancy with respect to the Mayo Clinic series. Younger patients, in fact, are more likely to develop malignant transformation during their lifetime, because they are at risk for a longer time.

A number of studies have investigated the rate of progression and risk factors predicting malignant evolution (Table 4). The results of these studies are variable, probably due to differences in sample size and follow-up duration, or to patient selection. The actuarial probability of progression ranges from 12% to 17% at 10 years, 25% to 34% at 20 years, and 30% to 39% at 25 years. However, since MGUS is a condition typical of advanced age, the majority of patients die from other diseases before malignant progression occurs. In fact, when competing causes of death are taken into account, the actual rate of progression at 25 years in the Mayo Clinic series is 11.2%.[11] In a large prospective study, using a competing risk model with death without transformation as competing event, the risk of transformation of MGUS into multiple myeloma or lymphoproliferative disorder was 3.9% at 10 years, corresponding to an annual rate of progression of 0.4%.[18]

In the current study, the size of M-protein, hemoglobin levels and percentage of BMPC were independent risk factors for progression. The prognostic value of the size of M-protein at diagnosis has been clearly recognized in previous studies.[2,5,7,11,16] More recently, Rosiñol et al[16] showed that the risk of progression depends not only on the initial size of the M-protein, but also on its evolution during the first 3 years of follow-up. In fact, patients with a progressive increase of serum M-protein (so-called evolving MGUS), which represent about 10% of all patients, have an actuarial probability of transformation of 55% at 10 years and 80% at 20 years, compared to 10% and 13%, respectively, for patients with non-evolving MGUS.[16]

Rajkumar et al[15] demonstrated that an abnormal FLC ratio is an independent risk factor for progression, regardless of type and size of serum M-protein. Patients with non-IgG MGUS, serum M-protein of 1.5 g/dL or more, and an abnormal serum FLC ratio had a risk of progression of 58% compared with 5% for patients with none of these factors. In the current study we could not evaluate the role of FLC as a risk factor for progression due to the short follow-up of patients for whom this parameter was available. In our series, the percentage of BMPC at diagnosis was associated with a higher risk of progression, in

keeping with the few other studies in which bone marrow aspiration was systematically performed at diagnosis.[2,5,16]

The prognostic relevance of hemoglobin levels has been previously demonstrated in asymptomatic IgM gammopathies[13] and more recently in a study on IgA and IgG MGUS.[17] In the current series, hemoglobin retains its prognostic role in multivariate analysis, suggesting that it does not depend only on the extent of BM infiltration. It might be hypothesized that anemia of chronic disease may be present in MGUS patients at higher risk of progression.

The main purpose of this study was to evaluate whether the pattern of presentation and the outcome of MGUS have changed over time. With this aim, we divided patients into 3 groups by the date of diagnosis. Diagnostic techniques for the detection of monoclonal component have changed during this time, and we are aware that this could represent a limitation of the study. However, in comparing groups, we analyzed not just the concentration of monoclonal component at diagnosis, but the overall pattern of clinical presenting features.

The clinical characteristics of MGUS patients at presentation have changed over the last 30 years. There is no evident explanation for the increase of IgM MGUS from 6% to 15%; however, the proportions of patients with IgM MGUS in group I and group III are similar to those reported in 2 population-based studies performed in the same periods by Axelsson et al[1] and Kyle et al,[11] respectively. Moreover, there was a significant increase of serum hemoglobin and albumin, and a decrease of median levels of β_2-microglobulin, M-protein, and BMPC throughout the past 3 decades.

The number of patients diagnosed in the 3 decades is not homogeneous, increasing from 100 in the first decade up to 919 in the third decade. Since this is not a population-based study, we cannot conclude that the incidence of MGUS has changed over time, even though the increasing average age of the Italian population makes this hypothesis not unlikely. The increasing number of patients as well as the changing pattern of presentation could be due to the availability of more sensitive diagnostic techniques able to identify minimal monoclonal bands not detectable in the past, and to an increased tendency to perform screening analyses in healthy subjects.

The differences of some presenting features among groups, although statistically significant, are, in themselves, of little relevance from a clinical point of view. However, the changes of clinical characteristics taken together indicate that MGUS is now diagnosed earlier than in the past. About two-thirds of
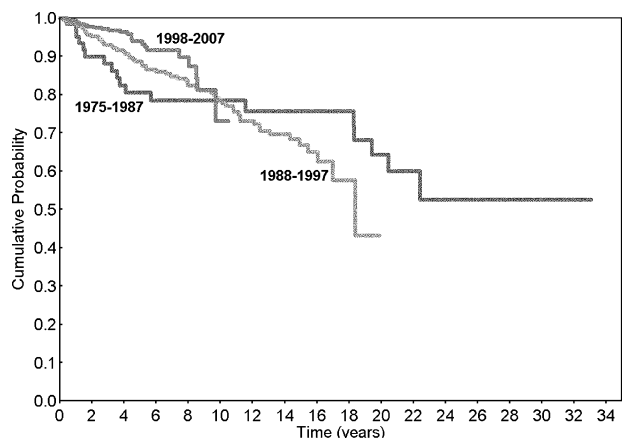

FIGURE 2. Risk of malignant transformation in patients with MGUS by period of diagnosis.

TABLE 4. Predictive Factors and Actuarial Probability of Progression in MGUS

Reference (First Author, Year)	No. of Patients	Risk Factors for Progression	Actuarial Probability of Progression (%)	
			10 Year	20 Year
Bladé, 1992[3]	128	IgA	19	-
Baldini, 1996[2]	386	M-protein size	-	-
		BMPC		
		Polyclonal Ig reduction		
Gregersen, 2001[7]	1247	M-protein size	13	-
		IgA		
		Female		
Kyle, 2002[11]	1384	M-protein size	12	25
		IgA or IgM		
Cesana, 2002[5]	1104	M-protein size	14	-
		BMPC		
		IgA or IgM		
		Detectable BJ proteinuria		
		High ESR		
		Polyclonal Ig reduction		
Rajkumar, 2005[15]	1148	M-protein size	9	20
		IgA or IgM, or IgA+IgM		
		Abnormal FLC ratio		
Rosiñol, 2007[16]	359	M-protein size	10 Non-evolving	13 Non-evolving
		BMPC	55 Evolving	80 Evolving
		IgA		
		Evolving type		
Schaar, 2009[18]	1007	M-protein size	3.9	-
		IgA or IgM		
Present report	1400	M-protein size	18	45
		Hb		
		IgA		

Abbreviations: BJ = Bence-Jones, ESR = erythrocyte sedimentation rate, Hb = hemoglobin, Ig = immunoglobulin.

patients diagnosed in our institution in the last decade had a serum M-protein at diagnosis lower than 1.5 g/dL. A large population-based study, performed on 21,463 Minnesota residents screened for a serum M-protein, found that the prevalence of MGUS is 3% over 50 years and 5% over 70 years. Among patients with a serum M-protein, its concentration was <1 g/dL in 63% of cases and ≤1.5 g/dL in 83%.[12]

This different pattern of presentation may have important implications for the outcome of MGUS patients. Most of these small components, in fact, were missed in the past and therefore are underrepresented in prior studies on the clinical significance of MGUS. Even though a longer follow-up is needed to confirm this finding, the probability of progression at 5 years for patients diagnosed in the last decade is lower compared to that in patients diagnosed before. If these results are confirmed at longer follow-up, the management of patients should be revised. To date, the current practice is to see patients once a year indefinitely. Go and Doyle[6] highlighted the potential harm of such a strategy. Actually, they found that the psychological distress of MGUS patients is similar to that of multiple myeloma patients, showing that the psychological burden of cancer anticipation can be disturbing.[6] The need for lifelong follow-up for patients with low-risk MGUS (serum IgG protein <1.5 g/dL with normal FLC ratio) has been questioned by Bladé et al,[4] in view of their very low probability of progression. On the other hand, the same

authors recommend a lifelong follow-up for high-risk patients (IgA or IgM, M-protein size >1.5 g/dL, abnormal serum FLC ratio), since their probability of malignant evolution is about 60% at 20 years. Evolving MGUS should be considered as an early myeloma rather than a true MGUS, thus requiring a close follow-up.[16]

Compared to a sex- and age-matched population, MGUS patients have reduced survival, as previously reported.[8,18,20] However, the life expectancy of MGUS patients with a M-protein lower than 1.5 g/dL is similar to that of the general population. A recent population-based study[10] conducted in Sweden showed that the excess mortality is more pronounced in elderly than in younger MGUS patients. Besides the expected increased risk of dying from multiple myeloma and lymphoproliferative disorder, MGUS patients were at increased risk of dying from bacterial infections and from heart, liver, and renal diseases.[10] In the current study, while the risk of progression of patients diagnosed in the last decade is lower compared to that of patients diagnosed in previous decades, the incidence of death remained stable over time, confirming the importance of competing causes of death in MGUS patients.[8,10,18]

In conclusion, we found that the pattern of presentation of MGUS has changed over time and now includes a higher proportion of patients with more favorable presenting features and probably a better outcome compared to the past. This changing

scenario calls for revising the current thinking on the clinical significance of MGUS and on the management of patients. The future direction could be the elaboration of risk-adapted follow-up guidelines, including the identification of a subset of patients who do not require follow-up.

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