Research Article

Cancer Epidemiology, Biomarkers & Prevention

Post-MGUS Diagnosis Serum Monoclonal-Protein Velocity and the Progression of Monoclonal Gammopathy of Undetermined Significance to Multiple Myeloma

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Abstract

Background: Multiple myeloma is a common hematologic malignancy consistently preceded by monoclonal gammopathy of undetermined significance (MGUS). Little is known about postdiagnosis clinical predictors of progression of MGUS to multiple myeloma to guide MGUS management. This study aimed to investigate whether the rate of rise in serum monoclonal protein concentration during the year after MGUS diagnosis—M-protein velocity—predicts progression of MGUS to multiple myeloma.

Methods: Data from the U.S. Veterans Health Administration system were used. A retrospective cohort of patients with MGUS who progressed to multiple myeloma were matched on age at MGUS diagnosis and race in a 1:4 ratio to the patients with MGUS using incidence density sampling. Kaplan–Meier curves were plotted. Univariable and multivariable conditional logistic regression analyses were fitted from the matched risk sets.

Results: A total of 128 cases and 490 matched controls were included. The case group contained a higher percentage of patients with M-protein velocity >0.1 g/dL/year than the control group (44.5% vs. 28.2%, $P<0.0001$). M-protein velocity of >0.1 g/dL during the year following MGUS diagnosis was positively associated with progression of MGUS to multiple myeloma (multivariable-adjusted odds ratio = 2.15; 95% confidence interval, 1.37–3.35).

Conclusions: Patients with a positive M-protein velocity during the year after MGUS diagnosis may be considered for more frequent monitoring for early detection and timely treatment of multiple myeloma. Future prevention studies could target these patients for intervention evaluation.

Impact: Our results suggest a new clinical predictor of progression to multiple myeloma following MGUS diagnosis, which has potential to identify high-risk patients for management and prevention.

Introduction

Multiple myeloma is one of the most common hematologic malignancies in the United States. In 2018, multiple myeloma accounts for 12,770 deaths, and 30,770 new multiple myeloma cases are expected (1). Multiple myeloma is characterized by clonal bone marrow plasma cells ≥10% or biopsy-proven bony or extramedullary plasmacytoma and evidence of end organ damage; or the presence of at least one of the following: ≥60% clonal plasma cells on bone marrow examination, serum involved/uninvolved free light chain ratio of ≥100, provided the absolute level of the involved light chain is ≥100 mg/L, or >1 focal bone lesion ≥5 mm in size (2).

Multiple myeloma is consistently preceded by monoclonal gammopathy of undetermined significance (MGUS; refs. 3, 4), a premalignant disorder defined by the presence of serum monoclonal protein (M-protein) of ≤3 g/dL, <10% bone marrow monoclonal plasma cell infiltrate, and the absence of end organ damage (5). The prevalence of MGUS in the population age ≥50 is ∼3% (6) with a 1% annual risk of progression to more advanced diseases, including multiple myeloma (7). Patients with MGUS are asymptomatic and a diagnosis of MGUS does not currently warrant treatment. Management of MGUS is restricted to monitoring for disease progression (8, 9). For patients with a measurable clonal immunoglobulin (Ig), some have recommended 2 to 3 serum protein electrophoresis tests for the first year after diagnosis and then one test every 2 to 3 years for low-risk patients or annually for intermediate and high-risk patients as long as there are no symptoms suggestive of progression (8, 9).

Previous studies reported that serum M-protein concentration ≥1.5 g/dL at MGUS diagnosis, Ig isotype other than IgG, an abnormal serum-free light-chain ratio, proportion of bone marrow aberrant plasma cells within the bone marrow plasma cell compartment ≥95% (7, 10), and reduced levels of 1 or 2 noninvolved Ig isotypes (11) are associated with progression of MGUS to multiple myeloma. Therefore, patients with MGUS who have one or more of these factors are classified as intermediate (1–2 risk factors) or high (≥3 risk factors) risk of progression and should be monitored annually for life (8, 9). However, to

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date, no studies have provided clear evidence that dynamic factors measured after MGUS diagnosis can refine the prognostication, and ultimately management of MGUS. Because serum M-protein at MGUS diagnosis is used as a marker of disease burden in patients with multiple myeloma (7), it is logical that increasing M-protein levels could foreshadow progression to multiple myeloma. Thus, a better understanding of M-protein level changes following MGUS diagnosis could provide insights into the expected natural history of patients with MGUS.

The objective of this study is to investigate whether the rate of rise in M-protein concentration—M-protein velocity—during the year following MGUS diagnosis can predict the progression of MGUS to multiple myeloma in patients diagnosed with MGUS.

Materials and Methods

Data, study population, and design

We used the International Classification of Diseases, 9th Revision, Clinical Modification (ICD-9-CM) codes to identify MGUS (273.1) and multiple myeloma (203.0) diagnoses in the United States Veterans Health Administration (VHA) system database. To confirm multiple myeloma diagnosis, we further used the International Classification of Diseases for Oncology code 9732/3 to identify patients in the Veterans Affairs Central Cancer Registry, including only those who received MM treatment within 6 months of multiple myeloma diagnosis. Furthermore, patient charts were reviewed to verify MGUS and multiple myeloma diagnoses following the criteria defined by the International Myeloma Working Group (1, 5). During chart review, MGUS and multiple myeloma diagnoses as well as the date of diagnoses were confirmed; furthermore, all available levels of M-protein concentration, Ig isotype as determined by immunofixation electrophoresis, and dates of M-protein measurements were obtained. Two reviewers (JG and TST) independently reviewed patient charts, abstracted data, and resolved disagreements by consensus.

We identified 9,287 patients with $\geq$2 ICD-9-CM codes for MGUS diagnosis between October 1, 1999 and December 31, 2009 in all 21 regional VHA districts throughout the United States (Fig. 1). The date of the first MGUS diagnosis was obtained through data abstraction. These patients were followed through August 6, 2013. Among them, 617 patients developed multiple myeloma. We excluded (i) 54 patients whose M-protein at MGUS diagnosis was unknown or measured before October 1, 1998; (ii) 52 patients whose M-protein at MGUS diagnosis was >3.0 g/dL, as these patients met criteria for smoldering multiple myeloma (SMM); (iii) 34 patients whose MGUS type was light-chain or Ig isotype other than IgG or IgA, because light-chain only disease cannot be measured by serum protein electrophoresis, IgM typically does not progress to multiple myeloma (11, 12), and IgD is rare (13); (iv) 194 patients, who had no M-Protein measurement within 14 months post-MGUS diagnosis except that at MGUS diagnosis and; (v) 119 patients whose multiple myeloma diagnosis was <2 years following MGUS diagnosis; and (vi) 36 patients, whose last M-protein was measured <6 months after MGUS diagnosis. We applied the same exclusion criteria on patients without a multiple myeloma diagnosis, except for (v), for which we excluded patients who died or were censored <2 years after MGUS diagnosis. Patients with multiple myeloma were then matched on age at MGUS diagnosis ($\leq$65, >65) and race (white, black, other, unknown) in a 1:4 ratio to the patients with MGUS with or without a diagnosis of multiple myeloma using incidence density sampling (14). In this sampling scheme, controls to an index case are selected with replacement from all patients at risk excluding the index case itself (including patients diagnosed with multiple myeloma at later times) at the event time of the index case (14). Finally, in the matching process, 9 cases were only able to match to <4 controls, resulting in 128 cases and 490 matched controls (204 patients with multiple myeloma and 286 patents without multiple myeloma) or 396 unique patients for the subsequent analyses.

Unique patient identifiers were used to obtain data on sex, race, height, weight, and comorbidities. The Romano adaptation of the Charlson comorbidity index was calculated based on comorbidities present before MGUS diagnosis (15). We computed body mass index (BMI) at MGUS diagnosis, weight in kilograms divided by the square of height in meters, and categorized as underweight (BMI <18.5), normal weight (BMI 18.5–24.9), overweight (BMI 25–29.9), or obese (BMI $\geq$30; ref. 16). We used the most frequently measured height for each patient and the weight measured one month before or after MGUS diagnosis, favoring the value closest to the date of MGUS diagnosis (17).

Institutional Review Boards at both Washington University School of Medicine and Veteran Affairs Saint Louis Healthcare System approved the study.

Exposure: 1-year post-MGUS diagnosis M-protein velocity

We defined exposure as 1-year post-MGUS diagnosis M-protein velocity. M-protein velocity was computed as the slope between the M-protein concentration values from the first and the last measurements during the year following MGUS diagnosis (g/dL/year), as follows:

$$\text{Velocity} = \frac{\text{Value at the last measurement} - \text{Value at MGUS diagnosis}}{\text{Months from MGUS diagnosis to last measurement}} \times 12.$$

M-protein velocities were further categorized into >0.1 and $\leq$0.1 g/dL/year. The cutoff of 0.1 was determined using all cases and controls (18–20), because it yielded the maximum of Youden J statistic (i.e., the sum of sensitivity and specificity; ref. 18).

Outcome measures

For Kaplan–Meier analyses, the outcome measure was time from MGUS diagnosis to multiple myeloma diagnosis, when present. The date for the first multiple myeloma diagnosis from data abstraction was used as the date of multiple myeloma diagnosis. Patients without a multiple myeloma diagnosis were censored at death or August 06, 2013, whichever came first. For univariable and multivariable conditional logistic regression analyses, the outcome measure was whether a patient had a multiple myeloma diagnosis.

Statistical analyses

Summary statistics of the demographic and clinical characteristics stratified by matched cases and controls were computed. To compare patients who progressed to multiple myeloma and patients who did not among the 396 unique patients, we used Chi-square tests to examine differences in proportions for categorical variables; for continuous variables, we used Student t tests to examine differences in means and Wilcoxon signed-rank tests to examine differences in medians.

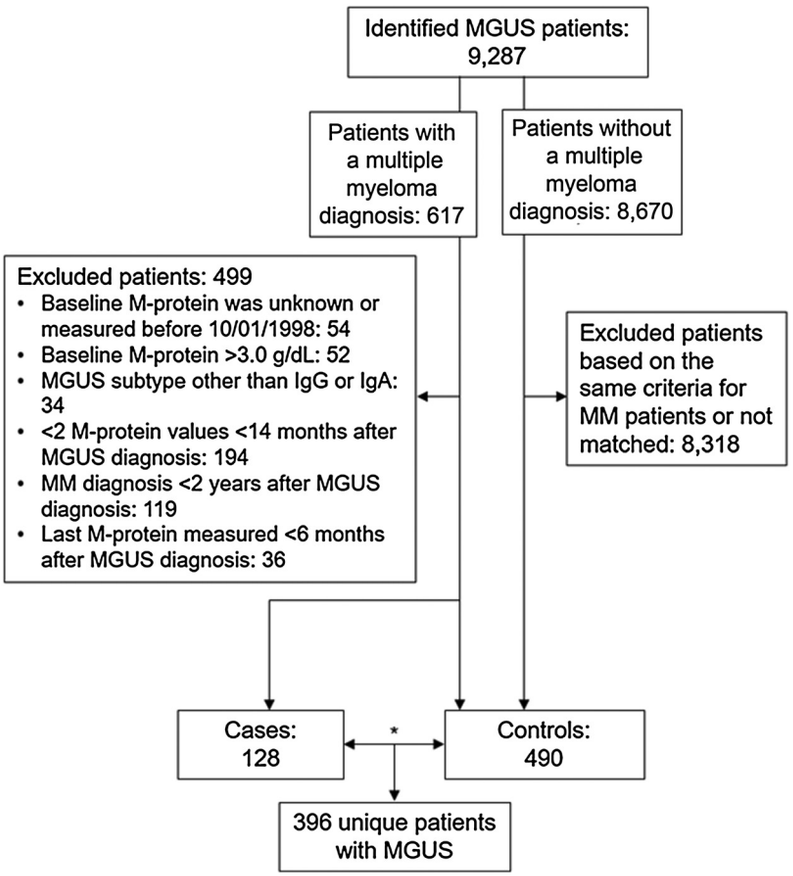

Figure 1.
Consort diagram for the matched cases and controls. *, 1:4 matching on age at MGUS diagnosis and race using incidence density sampling. In this sampling scheme, controls to an index case are selected with replacement from all patients at risk (including patients diagnosed with multiple myeloma at later times) at the event time of the index case, excluding the index case itself. Therefore, the selected controls can include patients who developed multiple myeloma later. The analytic cohort included 396 unique patients (128 unique cases and 490 controls).

Kaplan–Meier curves were plotted on 396 unique patients to compare the progression time to multiple myeloma between patients with velocity $\leq$0.1 g/dL/year and patients with velocity >0.1 g/dL/year. A stratified log-rank test for the matched cases and controls was performed to detect the statistical difference between the 2 groups.

Univariable and multivariable conditional logistic regression analyses fitted from the matched risk sets were performed (21). We included the following covariates: 1-year post-MGUS diagnosis velocity (>0.1, $\leq$0.1 g/dL/year), Ig isotype (IgA, IgG), sex (male, female), BMI group (underweight, normal weight, overweight, obese, unknown), age, Charlson comorbidity index, and M-protein concentration at MGUS diagnosis. We also used 1-year post-MGUS diagnosis velocity as a continuous covariate in both univariable and multivariable conditional logistic regression analyses.

All tests were 2-sided. Statistical significance was determined by an alpha level of 0.05. All statistical analyses were performed using SAS version 9.2 (SAS Institute Inc.).

Results

This study included 396 unique patients diagnosed with MGUS between October 1, 1999 and December 31, 2009 (128 cases and 490 controls, due to the inclusion of patients with multiple myeloma in the selected controls). Mean age at MGUS diagnosis was 67 years in both cases and controls (Table 1). Patients were predominantly male (cases: 96.1%; controls: 96.9%). More than 60% of the patients were white (cases: 60.2% white, 29.7% black; controls: 61.4% white, 30.6% black) and either overweight or obese (cases: 31.3% overweight, 33.6% obese; controls: 39.0% overweight, 28.2% obese). Although we matched on race, proportion of white and black patients are not the same for cases and controls due to the 9 cases that were able to match fewer than 4 controls. Mean Charlson score at MGUS diagnosis was 2.7 for cases and 3.0 for controls. Mean M-protein concentration at MGUS diagnosis was 1.3 g/dL for cases and 0.8 g/dL for controls. M-protein velocity >0.1 g/dL during the first year following MGUS diagnosis was seen in 44.5% of the cases and 28.2% of the controls. A majority of patients had IgG (cases: 80.5%; controls: 87.6%). Finally, mean follow-up was shorter for cases than controls (60.2 months vs. 96.3 months). All of the aforementioned variables were not statistically significantly different between patients who developed multiple myeloma and patients who did not, except for mean M-protein concentration at MGUS diagnosis (P <0.0001), M-protein velocity >0.1 g/dL during the first year following MGUS diagnosis ($P = 0.0011$), Ig isotype ($P =$ 0.0092), and mean follow-up (P <0.0001).

The Kaplan–Meier curves (Fig. 2) show a significantly higher proportion of progression among patients with M-protein velocity >0.1 g/dL/year (dashed curve) with median time to multiple myeloma of 119 months, compared with patients with M-protein velocity $\leq$0.1 g/dL/year (solid curve) with median time not reached. Among patients who progressed to multiple myeloma, the median time to multiple myeloma for patients with M-protein velocity >0.1 g/dL/year was 44 months, and the median time to

Table 1. Demographic and clinical characteristics by matched 128 cases and 490 controls among 396 unique U.S. veterans diagnosed with MGUS between October 1, 1999 and December 31, 2009

Variable\Sample size	Overall 396[a]	Cases 128	Controls 490	*P* value[b]
Age at MGUS diagnosis, mean (SD) years	66.9 (9.6)	66.8 (9.9)	67.1 (9.0)	0.8034[c]
Year of MGUS diagnosis (median)	2004	2004	2004	0.7098[d]
Male (%)	96.2	96.1	96.9	0.6153[e]
Race (%)				0.9320[e]
White	59.3	60.2	61.4	
Black	31.3	29.7	30.6	
Other	0.8	1.6	0.2	
Unknown	8.6	8.6	7.8	
BMI group (%)				0.4584[e]
Underweight	1.0	0.0	1.4	
Normal weight	17.9	17.2	16.5	
Overweight	34.3	31.3	39.0	
Obese	30.6	33.6	28.2	
Unknown	16.2	18.0	14.9	
Comorbidities, mean Charlson score (SD)	3.0 (2.8)	2.7 (2.6)	3.0 (2.8)	0.1734[c]
Ig isotype (%)				0.0092[e]
A	13.1	19.5	12.5	
G	86.9	80.5	87.6	
M-Protein velocity during the year after MGUS diagnosis (%)				<0.0001[c]
≤0.1 g/dL/year	66.7	55.5	71.8	
>0.1 g/dL/year	33.0	44.5	28.2	
Serum M-protein concentration at MGUS diagnosis, mean (SD) g/dL	0.9 (0.7)	1.3 (0.7)	0.8 (0.6)	0.0011[c]
Follow-up, mean (SD) months	83.2 (36.9)	60.2 (29.5)	96.3 (35.2)	<0.0001[c]

[a]Incidence density sampling selects controls with replacement from all people (including patients with a diagnosis of multiple myeloma) at risk at the time of case occurrence, excluding the index case itself, so controls include patients with multiple myeloma. Therefore, the analytic cohort included only 396 unique patients (128 unique cases and 490 controls). Also see Fig. 1 for the consort diagram.

[b]Statistical tests were performed to compare differences between patients who progressed to multiple myeloma and patients who did not among the 396 unique patients.

[c]Student *t* test.

[d]Wilcoxon rank sum test.

[e]Chi-square test.

multiple myeloma for patients with M-protein velocity ≤0.1 g/dL/year was 59 months. The stratified log-rank test, P <0.0001, for the matched cases and controls showed a statistically significant difference between the 2 groups.

Table 2 presents crude odds ratios (OR) and multivariable-adjusted ORs (aOR) from the univariable and multivariable conditional logistic regression, respectively. For the multivariable analyses, M-protein velocity was dichotomized (left) or included as a continuous variable (right). In the multivariable analysis using dichotomized M-protein velocity (concordance index = 0.8475), M-protein velocity of >0.1 g/dL increase in the first year following MGUS diagnosis was positively associated with progression of MGUS to multiple myeloma [aOR = 2.15; 95% confidence interval (CI), 1.37–3.35; $P = 0.0008$]. A higher level of M-protein concentration at MGUS diagnosis (aOR = 5.03; 95% CI, 3.46–7.33; P <0.0001 per 1 g/dL increase) and IgA relative to IgG isotype (aOR = 4.11; 95% CI, 2.25–7.52; P <0.0001) were positively associated with progression to multiple myeloma. BMI group, age, and Charlson comorbidity index at MGUS diagnosis were not statistically significantly associated with progression to multiple myeloma. In the multivariable analysis using M-protein velocity as a continuous variable (concordance index = 0.8455), each 1 g/dL increase in M-protein velocity during the year following MGUS diagnosis was associated with a 115% increase in the odds of progression to multiple myeloma (aOR = 2.15; 95% CI, 1.24–3.72; $P = 0.0066$ per 1 g/dL increase).

Discussion

To our knowledge, this study is the first to examine the association between M-protein velocity during the first year following MGUS diagnosis and progression to multiple myeloma. We observed that independent of the known risk factors, a positive M-protein velocity during the year after MGUS diagnosis was associated with a >2-fold increase in the odds of progression to multiple myeloma. This finding is important in that it identifies a new clinical predictor of progression to multiple myeloma following MGUS diagnosis, in addition to the existing ones.

Our finding is partially consistent with that of a previous study, which observed that the evolutionary pattern of M-protein during the first 3 years of follow-up is the most important risk factor for

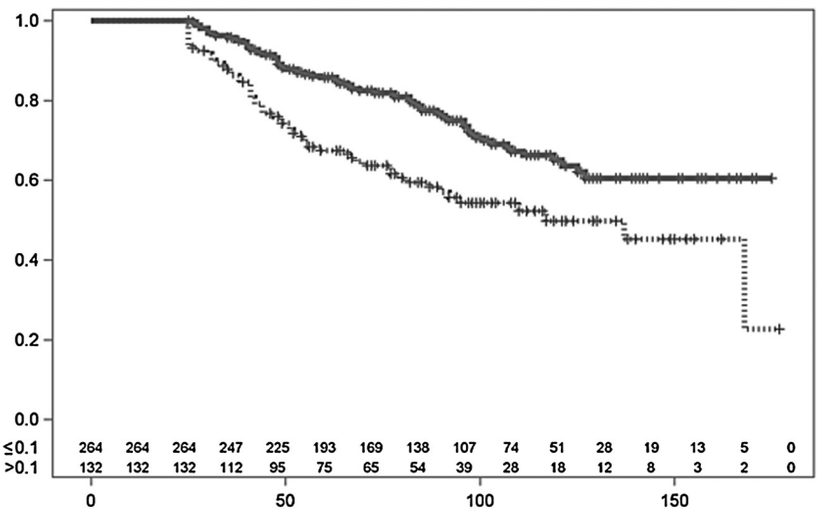

Figure 2.
Kaplan–Meier curves for progression to multiple myeloma on 396 unique patients with MGUS by 1-year post-MGUS diagnosis M-protein velocity. Horizontal axis label: Months from MGUS diagnosis. Vertical axis label: Proportion without progression to multiple myeloma. + Censored. Solid curve: Post-MGUS diagnosis M-protein velocity ≤0.1 g/dL/year. Dashed curve: Post-MGUS diagnosis M-protein velocity >0.1 g/dL/year. Stratified log-rank test: P <0.0001.

Table 2. Univariable and multivariable-adjusted ORs for developing multiple myeloma among the matched 128 cases and 490 controls

	Univariable matched analyses		Multivariable matched analyses			
Covariate	**OR (95% CI)**	***P* value**	**aOR (95% CI)**	***P* value**	**aOR (95% CI)**	***P* value**
1-year post-MGUS diagnosis M-protein velocity (g/dL/year)					2.15 (1.24–3.72)	0.0066
≤0.1 g/dL/year	1.00 (referent)	–	1.00 (referent)	–	–	–
>0.1 g/dL/year	2.48 (1.71–3.60)	<0.0001	2.15 (1.37–3.35)	0.0008	–	–
Baseline serum M-protein (1 g/dL)	4.20 (3.01–5.83)	<0.0001	5.03 (3.46–7.33)	<0.0001	5.09 (3.50–7.40)	<0.0001
Ig isotype						
G	1.00 (referent)	–	1.00 (referent)	–	1.00 (referent)	–
A	1.85 (1.15–2.98)	0.0119	4.11 (2.25–7.52)	<0.0001	3.88 (2.14–7.03)	<0.0001
BMI group						
Normal weight	1.00 (referent)	–	1.00 (referent)	–	1.00 (referent)	–
Overweight	0.92 (0.54–1.56)	0.7606	0.79 (0.42–1.47)	0.4524	0.80 (0.43–1.50)	0.4910
Obese	1.36 (0.80–2.32)	0.2591	1.49 (0.79–2.84)	0.2217	1.51 (0.80–2.85)	0.2088
Sex						
Male	1.00 (referent)	–	1.00 (referent)	–	1.00 (referent)	–
Female	0.69 (0.24–1.97)	0.4915	0.34 (0.08–1.33)	0.1202	0.38 (0.10–1.45)	0.1555
Comorbidity score	0.96 (0.90–1.03)	0.2094	1.02 (0.94–1.11)	0.6414	1.02 (0.94–1.11)	0.5799
Age	0.99 (0.92–1.06)	0.7454	1.00 (0.92–1.09)	0.9925	1.00 (0.92–1.08)	0.9464
C-Index			0.8472		0.8455	

NOTE: –, reference group, estimate not available.

disease progression in 359 patients with MGUS in a single institution (22). Although similar in the conclusion that rising serum M-protein after MGUS diagnosis is an important predictor of the disease progression, our study improves upon their study in several ways. First, they categorized MGUS into nonevolving MGUS versus evolving MGUS, defined as a progressive increase in the M-protein concentration in each of the annual consecutive measurements during the first 3 years after MGUS diagnosis, while we computed velocity based on M-protein concentration measured in the first year following diagnosis to provide a more clinically practical and meaningful period to observe an indicative pattern of M-protein. Second, their outcome, although not explicitly defined, appeared to be time from 4th year postdiagnosis to multiple myeloma diagnosis/censoring to any transformation to a symptomatic disease, including multiple myeloma and Waldenström macroglobulinemia, whereas the outcome of our study focused on progression of multiple myeloma only. As transformation increases with age/time and may increase exponentially for patients of the evolving type, they found that evolving type is "the most important" risk factor for progression; while we found a positive velocity in the first year following diagnosis as "a risk factor among several risk factors." Interestingly, a much lower hazard ratio [HR = 5.1; 95% CI, 3.4–7.6 (23), relative to previously reported 12.1; 95% CI, 5.8–25.4 (22)] for evolving type (defined as a progressive increase of ≥10% in the M-protein during the year following SMM diagnosis when M-protein at MGUS diagnosis was ≥3 g/dL or a progressive increase in M-protein in each of the annual measurements when M-protein at MGUS diagnosis was <3 g/dL) was found in a recent study of 206 patients diagnosed with SMM in a single institution in Spain (23). Despite this, several studies pointed out that "evolving MGUS" potentially could be a marker for an early multiple myeloma with a slow rate of progression, although this has not been confirmed (4, 24). Our study supports this. Furthermore, comparable to the finding of a study that evaluated stored biospecimens in patients later diagnosed with multiple myeloma, which found that nearly half of the patients with multiple myeloma had year-by-year increase in M-protein before multiple myeloma diagnosis, whereas the other half had a stable pattern (4), our study finds that nearly 45% of the cases had a positive velocity during the first year of MGUS diagnosis, whereas 55% did not.

Past studies concluded that M-protein concentration ≥1.5 g/dL at MGUS diagnosis is the most important risk factor of progression of MGUS to multiple myeloma (9, 12). However, no predictor has been found beyond the diagnosis of MGUS to further guide the management of MGUS. Our study found that a positive M-protein velocity during the year after MGUS diagnosis significantly impacted progression of MGUS to multiple myeloma, in addition to M-protein concentration at diagnosis. Our study enhances the current risk stratification and has 2 clinical implications. First, MGUS patients with a positive M-protein velocity during the first year following MGUS diagnosis should consider a more frequent monitoring plan, regardless of the level of M-protein concentration at diagnosis. This could lead to a more timely diagnosis and earlier treatment of multiple myeloma, potentially resulting in better multiple myeloma survival (25). Second, with advancement in the potential treatments in patients with high-risk SMM (26, 27) and possibly in high-risk patients with MGUS (13, 28), M-protein velocity could help identify the patients with high-risk MGUS appropriate for intervention. Finally, if a preventive treatment were available for patients with MGUS, it is conceivable that reduction in M-spike velocity (or reduction of M-spike concentration in general) could serve as a surrogate marker to measure the efficacy of such a therapy.

M-protein level is currently used to measure response and progression in patients with active multiple myeloma, as it is highly correlated with disease burden. Similarly, M-protein velocity is associated with progression of MGUS to multiple myeloma, a process generally associated with expansion of clonal plasma cells. Currently, prospective studies of MGUS or low-risk SMM are not viable due to the low event rate, which requires large numbers of patients followed for a long period of time to achieve adequate statistical power. Thus, there is significant value in the identification of an easily measured biomarker that could be considered a surrogate for efficacy in the prevention setting.

Our study is somewhat different from studies in prostate cancer that used prostate-specific antigen (PSA) velocity during the year before a prostate cancer diagnosis as a prognostic marker (29, 30). They found that men with increasing PSA levels of >2.0 ng/mm in the year before diagnosis had a higher risk of death from prostate cancer despite undergoing radical prostatectomy (30) or external beam radiation therapy (29). Although there is value in using

biomarkers to improve prognostication, predictive biomarkers offer greater value as there is potential for intervention before the devastating disease.

Our study has several strengths. Through patient chart review, we verified MGUS and multiple myeloma diagnoses and the dates of diagnoses by reviewing patients' charts, instead of only relying on ICD-9-CM codes and diagnosis dates in the administrative database to ensure accuracy of the data. Moreover, through chart review, we were able to determine MGUS subtype and levels of serum M-protein concentration. Furthermore, to avoid predicting multiple myeloma diagnosis using levels of M-protein measured too close to the development of multiple myeloma, we only used those measured $\leq$1 year post-MGUS diagnosis and excluded patients whose multiple myeloma diagnosis was <2 years following MGUS diagnosis. Finally, despite the relatively uncommon outcome of multiple myeloma, the large number of patients in the national VHA database provided sufficient statistical power to form cases and controls to study this association.

Our study also has limitations. First, patients served by the VHA are frequently from older age, predominately male sex, and lower socioeconomic background (31–33). If these characteristics of the population influence the diagnoses of MGUS or multiple myeloma, then our conclusion may not be generalizable to broader populations with MGUS. Second, we noticed a lower mean comorbidity score at MGUS diagnosis in the cases than in the controls, although not statistically significant. Our estimates could overestimate the magnitude of the true association between M-protein velocity and transformation to multiple myeloma, because more comorbidities among controls could result in a higher death rate, and thus a higher likelihood of censoring due to death before multiple myeloma diagnosis. For this, we would expect the odds ratio for comorbidity scores to be <1. Nonetheless, the results do not show any evidence of this. Finally, although we designed our study to minimize potential biases, some sources of bias from unmeasured confounders could remain. For example, incidence-prevalence bias may exist. Including patients whose MGUS diagnosis was not truly incident (due to the fact that patients with MGUS are asymptomatic) may overestimate the true association of velocity. This happens because the computed velocity is based on the year following MGUS diagnosis rather than the year following MGUS incidence. If MGUS had already progressed to multiple myeloma during the year after MGUS diagnosis, then the M-protein velocity would be higher due to multiple myeloma, falsely increasing the estimated association would be stronger. Conversely, excluding patients with a diagnosis of multiple myeloma $\leq$2 years after MGUS diagnosis may underestimate the true association, because these patients may represent the patient subpopulation with highest risk of disease progression.

Conclusions

Our study demonstrated that an M-protein velocity >0.1 g/dL during the year following MGUS diagnosis is associated with a higher risk of progression to multiple myeloma. More frequent monitoring could be considered in these patients to allow for early detection and timely diagnosis of multiple myeloma. Future studies could target these patients for evaluation of preventative interventions.

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

Disclaimer

The conclusions and opinions presented herein are solely the responsibility of the authors and do not necessarily represent the official views of the NIH, the Agency for Healthcare Research and Quality, the American Cancer Society, or the Foundation for Barnes-Jewish Hospital.

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Analysis and interpretation of data (e.g., statistical analysis, biostatistics, computational analysis): S-H. Chang, J. Gumbel, S. Luo, T.S. Thomas, K.M. Sanfilippo, J. Luo, G.A. Colditz, K.R. Carson
Writing, review, and/or revision of the manuscript: S-H. Chang, J. Gumbel, T.S. Thomas, K.M. Sanfilippo, G.A. Colditz, K.R. Carson
Administrative, technical, or material support (i.e., reporting or organizing data, constructing databases): S-H. Chang, J. Gumbel, G.A. Colditz, K.R. Carson
Study supervision: S-H. Chang, G.A. Colditz, K.R. Carson

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