Immunoparesis and monoclonal gammopathy of undetermined significance are disassociated in advanced age

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Immunoparesis and a skewed serum free light chain (FLC) ratio are indicators of immune dysfunction predictive of progression from monoclonal gammopathy of undetermined significance (MGUS) to multiple myeloma (MM). Previous studies have reported increased prevalence of MGUS by age, but no study has examined the relationship between immunoparesis and abnormal FLC ratios in the elderly. We screened 453 older adults (median age, 80 years; range, 65–96) to characterize the patterns of immunoparesis and abnormal FLC ratio in relation to MGUS. We defined MGUS in 4.4% of the subjects; the prevalence was 12.5% among individuals of >90 years. In MGUS (vs. non-MGUS) cases, immunoparesis and abnormal FLC ratios were detected in 70.0% (vs. 49.0%; $P = 0.07$) and 50.0% (vs. 12.9%; $P = 0.0001$), respectively. Based on small numbers, MGUS patients with abnormal FLC ratio were borderline ($P = 0.07$) more likely to have immunoparesis. Overall, the prevalence of immunoparesis varied in a nonlinear fashion, with lowest frequencies in the youngest and oldest groups. Our observed disassociation between MGUS prevalence and impaired immunoglobulin production suggests that separate mechanisms are involved in the development of MGUS and immunoparesis in advanced age. These findings emphasize the need for molecularly defined methods to characterize myeloma precursor states and better predict progression to MM. Am. J. Hematol. 88:89–92, 2013. © 2012 Wiley Periodicals, Inc.

Introduction

Advanced age is associated with altered immune function and increased incidence of cancer, and there is evidence for interaction between these phenomena [1]. The plasma cell malignancy multiple myeloma (MM) is primarily a disease of older people, with median age at diagnosis of approximately 70 years [2]. MM consistently evolves from the precursor state monoclonal gammopathy of undetermined significance (MGUS) [3], characterized by production of a clonal immunoglobulin, and diagnosed by finding of a narrow monoclonal protein band on serum or urine protein electrophoresis. The Mayo Clinic has determined the prevalence of MGUS to be approximately 3% in whites aged 50 years or older [4], and in follow-up studies has reported serum free light chain (FLC) abnormalities to be present in this group among persons with and without "conventional" heavy-chain MGUS, increasing the overall prevalence of MGUS to approximately 4% [5].

Results from several population-based studies have shown that the prevalence of MGUS increases with age [4–7]. As indicated by its name, MGUS is associated with an uncertain risk of progression to MM and related disorders [8], and clinical markers of immune dysfunction including immunoparesis (uninvolved immunoglobulin levels below the lower limit of normal) and skewed serum FLC ratio have been proposed as significant indicators to predict progression to malignant disease [9,10]. Racial and ethnic characteristics have been shown to play a role in immunoglobulin production [11] and incidence of plasma cell dyscrasias [2,12], but there is limited information on the role of advanced age in these conditions. To further investigate the patterns of immunoparesis and altered immunoglobulin production in advanced age, we have conducted a screening study in a group of older adults ($n = 453$; age, $\geq$65 years), with a median age of 80 years.

Methods

Blood samples ($n = 453$) were included from a prior study [13] that evaluated persons aged $\geq$65 years at Mount Sinai Hospital, New York City, from February to December 2000. The study over-sampled Jewish subjects to examine correlates of human herpes virus-8 infection. Following a uniform protocol, subjects answered questions regarding demographic information and medical history and provided a blood sample. The informed consent was obtained from the participated subjects. This study was approved by institutional review boards at the National Cancer Institute and Mount Sinai Hospital. Briefly, plasma and cells were separated by the prior investigators within 24 hr of phlebotomy and stored at -70°C. Following all analyses for the prior study, samples were transferred to our institution via cold storage.

At our laboratory, samples were subjected to protein electrophoresis using a Helena SPIFE 3000 system (Helena Laboratories, Beaumont, TX). Gels were scanned on a V7000 scanner with Helena Laboratories software for identification and quantification of M-protein. Kappa and lambda FLC values were measured with a SPAplus specialist protein analyzer (The Binding Site, Birmingham, United Kingdom), and FLC ratios outside our reference range (0.26–1.65) were considered abnormal. Samples that demonstrated an M-protein band or abnormal FLC ratio were subjected to immunofixation electrophoresis. Samples that demonstrated clonality were classified as MGUS, and major immunoglobulin isotypes (i.e., IgG, IgA, and IgM) were quantified for all samples. Immunoglobulins were quantified using a SPAPlus automated analyzer (The Binding Site, Birmingham, United Kingdom). Per the manufacturer (using nonparametric statistics and representing 95% of the central population), the reference ranges are as follows: IgG: 610–1616; IgA: 84–499; and IgM: 35–242. Immunoparesis was defined as one or more immunoglobulins less than the lower limit of normal for

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TABLE I. Prevalence of MGUS, Immunoparesis, and Abnormal FLC Ratio in 453 Elderly Persons by Age, Sex, and Race

Parameter	Total no.	No. w/MGUS	Prevalence % (95% CI)	No. w/immunoparesis[a]	Prevalence % (95% CI)	No. w/abnormal FLC ratio[b]	Prevalence % (95% CI)
Total (all patients)	453	20	4.4 (2.7–6.7)	226	49.9 (45.2–54.6)	66	14.6 (11.5–18.2)
Age (y)							
65–70	40	2	5.0 (0.6–16.9)	17	42.5 (27.0–59.1)	4	10.0 (2.8–23.7)
70–75	86	2	2.3 (0.3–8.1)	39	45.3 (34.6–56.5)	12	14.0 (7.4–23.1)
75–80	103	2	1.9 (0.2–6.8)	53	51.5 (41.4–61.4)	12	11.7 (6.2–19.5)
80–85	105	6	5.7 (2.1–12.0)	59	56.2 (46.2–65.9)	18	17.1 (10.5–25.7)
85–90	79	3	3.8 (0.8–10.7)	41	51.9 (40.4–63.3)	12	15.2 (8.1–25.0)
>90	40	5	12.5 (4.2–26.8)	17	42.5 (27.0–59.1)	8	20.0 (9.1–35.6)
Sex							
Male	150	7	4.7 (1.9–9.4)	71	47.3 (39.1–55.6)	21	14.0 (8.9–20.6)
Female	303	13	4.3 (2.3–7.2)	155	51.2 (45.4–56.9)	45	14.9 (11.0–19.4)
Race							
White	300	14	4.7 (2.6–7.7)	168	56.0 (50.2–61.7)	34	11.3 (8.0–15.5)
Black	106	5	4.7 (1.5–10.7)	44	41.5 (32.0–51.5)	27	25.5 (17.5–34.9)
Hispanic	41	1	2.4 (0.1–12.9)	13	31.7 (18.1–48.1)	5	12.2 (4.1–26.2)
Other	6	0	0	1	16.7 (0.4–64.1)	0	0

[a] Immunoparesis defined as one or more of IgG, IgA, or IgM less than the lower limit of normal per our laboratory reference range (**Methods** section).
[b] Abnormal FLC ratio defined as outside the reference range (0.26–1.65) for our laboratory.

TABLE II. Prevalence of Immunoparesis and Abnormal FLC Ratios in 453 Elderly Persons by MGUS Status

Parameter	MGUS N, Prevalence % (95% CI)	Non-MGUS N, Prevalence % (95% CI)	*P*-value
Total number	20	433	
Median age (years)	82.0	79.7	
Abnormal FLC ratio	10	56	
	50.0 (27.2–72.8)	12.9 (9.9–16.5)	
Normal FLC ratio	10	377	0.0001
	50.0 (27.2–72.8)	87.1 (83.5–90.1)	
Immunoparesis	14	212	
	70.0 (45.7–88.1)	49.0 (44.2–53.8)	
No immunoparesis	6	221	0.07
	30.0 (11.9–54.3)	51.0 (46.2–55.8)	
Both immunoparesis and abnormal FLC ratio	9	28	
	45.0 (23.1-68.5)	6.5 (4.3-9.2)	
No immunoparesis, normal FLC ratio	5	193	<0.0001
	25.0 (8.7–49.1)	44.6 (39.8–49.4)	

our laboratory's respective reference range. Statistical calculations were performed using Microsoft Excel and IBM SPSS Statistics 20; all significance tests were two-tailed unless otherwise specified.

Results

Among the 453 individuals who were ≥65 years of age, 150 (33.1%) were males and 303 (66.9%) were females, with ages ranging from 65.1 to 95.7 years and a median age of 79.9 years. Racial makeup of the group was 300 (66.2%) white, 106 (23.4%) black, 41 (9.1%) Hispanic, and 6 (1.3%) other race. The findings of MGUS, immunoparesis, and abnormal FLC ratio among all 453 persons are summarized in Table I.

Monoclonal gammopathy of undetermined significance

Overall, we found 4.4% of samples to meet criteria for MGUS. The median ages in the MGUS and non-MGUS groups were 82.0 and 79.7 years, respectively; other comparisons are summarized in Table II. Eighteen cases (90%) of MGUS consisted of a single paired heavy-light chain monoclonal protein, and in two cases (10%), two monoclonal proteins were identified. The distributions of gammaglobulin isotypes IgG, IgA, and IgM were 55, 14, and 32%, respectively.

The prevalence of MGUS was similar between men (4.7%) and women (4.3%) and increased by age, with a prevalence of 12.5% among persons older than 90 years (Fig. 1). Overall, MGUS was present in 4.7% of samples from whites, 4.7% of samples from blacks, and 2.4% of samples from Hispanics. Among patients with MGUS, the prevalence of abnormal FLC ratio was 50.0%, and the prevalence of immunoparesis was 70.0%. Based on small numbers, MGUS patients with abnormal FLC ratio were borderline ($P = 0.07$) more likely to also have immunoparesis (Table III).

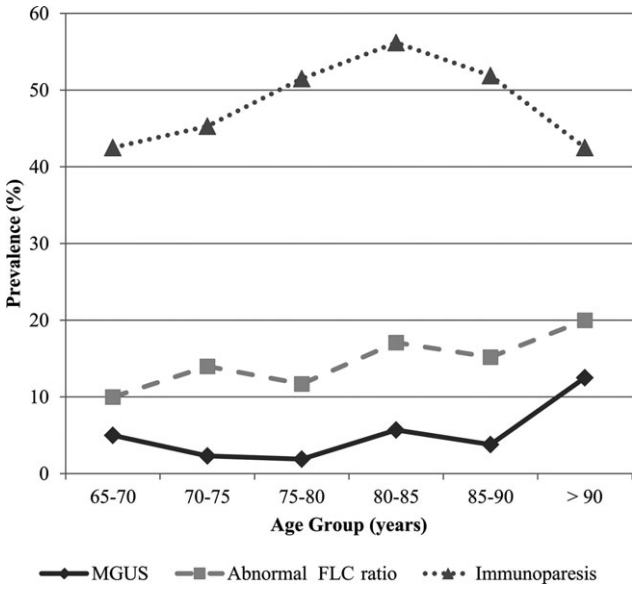

Figure 1. Prevalence of MGUS, abnormal FLC ratio, and immunoparesis among 453 elderly persons.

Immunoparesis

The overall prevalence of immunoparesis was 49.9%, and prevalence was similar between men (47.3%) and women (51.2%). The prevalence of immunoparesis across age groups followed a nonlinear pattern (Fig. 1). Prevalence was lowest in the youngest (65–70 years) and oldest (>90 years) age groups at 42.5%, and was highest among persons aged 80–85 years at 56.2%. Immunoparesis was detected among 56.0% of whites, 41.5% of blacks, 31.7% of Hispanics, and 16.7% among samples designated as other race. Among non-MGUS cases with immunoparesis ($n = 212$), we found depression of one, two, or three immunoglobulins in 144, 57, and 17 cases, respectively. The IgG, IgA, and IgM isotype was depressed in 65, 27, and 48% of these non-MGUS cases, respectively.

TABLE III. Immunoparesis Among 20 Elderly Persons With MGUS and With the Presence or Absence of Abnormal FLC Ratio

Parameter	MGUS with abnormal FLC ratio	MGUS without abnormal FLC ratio	*P*-value
Total number	10	10	
Immunoparesis	9	5	
No immunoparesis	1	5	0.07[a]

[a] Fisher exact (one-tailed) test.

Immunoparesis was identified in 70.0% of MGUS samples and in 49.0% of non-MGUS samples, and there was a trend toward an association of immunoparesis and MGUS ($P = 0.07$).

Abnormal FLC ratio

The overall prevalence of abnormal FLC ratio was 14.6%, and prevalence was similar between men (14.0%) and women (14.9%). The prevalence of abnormal FLC ratio doubled from 10.0% in the youngest age group (65–70 years) to 20.0% in the oldest age group (>90 years). Abnormal FLC ratios were found among 11.3% of whites, 25.5% of blacks, and 12.2% of Hispanics. Abnormal FLC ratios were present in 50.0% of MGUS samples and in 12.9% of non-MGUS samples, and this comparison was highly significant ($P = 0.0001$). Similar to the original study by Rajkumar et al. [10], showing that an abnormal FLC ratio is a significant predictor of progression to MM, kappa-to-lambda FLC ratios outside our reference range (0.26–1.65) were considered abnormal. A small proportion of cases (9%) with an abnormal FLC ratio were owing only to the suppression of one of the two light chains. The remaining 91% were owing to the relative elevation of one of the two light chains.

Discussion

This study of older adults (≥65 years; median age, 80 years) expands on prior investigations, showing that the prevalence of MGUS increases by age [4–7]. In our oldest age group including people older than 90 years, the prevalence of MGUS was 12.5%. The oldest age group (>80 years) reported by the Mayo Clinic had an MGUS prevalence of 6.6% [4]. We found the prevalence of MGUS to be 4.7% for both blacks and whites, in contrast to a previous large study that showed a threefold higher age-adjusted prevalence of MGUS for blacks relative to whites [12]. However, racial disparities in gammopathies are most pronounced in younger people and become less apparent with age [2], which may partly explain our finding of similar MGUS prevalence in this older population of whites (median age, 80.7 years) and blacks (median age, 78.4 years).

The previous studies of immune function in aging have focused on the changes in hematopoietic stem cells, immune organs, and T-cell functionality [14–17], but to our knowledge this is the first systematic investigation of immune changes in advanced age by the analysis of immunoglobulin production patterns. Immunoparesis was highly prevalent (49.9%) in our sample and interestingly, our results showed an inverted "U" pattern in which prevalence of immunoparesis was lowest in the youngest age group (65–70 years) at 42.5%, peaked at 56.2% in the 80–85 age group, and declined successively to 42.5% in the oldest age group (>90 years). Genetic [17] and microenvironmental [18] factors related to aging may be responsible for the changes in hematopoietic stem cell populations that select for myeloid precursor cells and result in a relative decrease of lymphoid progenitors, and centenarian studies have shown that the linear decline of lymphocyte numbers continues with advancing age [19]. However, studies of these "oldest old" have also found that rates of metabolic, inflammatory, and immune dysfunction decrease in very old age [20,21]. Our observation that immunoparesis peaks with advancing age but declines among very old individuals adds to our evolving understanding of the relationship between immune cell number and function in the very old.

There was a racial disparity in the prevalence of immunoparesis, which was present in 56.0% of samples from whites and 41.5% of samples from blacks. The original study sample [13] was enriched for Ashkenazi Jewish individuals, a group genetically predisposed to the development of autoimmune and other diseases [22], and this may partly explain the disparity observed in our study. Other differences in baseline immunoglobulin production have been reported across racial groups [11], and we were not able to provide molecular details to further characterize these differences.

The overall prevalence of abnormal FLC ratio was 14.6% in our sample compared to 3.3% in a prior population-based study of light-chain abnormalities [5]. Among persons with MGUS, we found an abnormal FLC ratio in 50%, an increase from the 33% prevalence reported by the Mayo Clinic [10]. Individuals with and without MGUS in our study were older (median ages of 82 and 80 years, respectively) than those in the Mayo conventional and light-chain MGUS studies (median ages of 72 and 70 years, respectively), and the increased prevalence of abnormal FLC reported here may be owing to increasing plasma cell dysfunction in advancing age or to the effect of an age-related factor. Renal disease, for example, may differentially alter kappa and lambda excretion rates, significantly influencing both levels of circulating light chains [23,24] and the FLC ratio. Such an age-related factor may work in concert with plasma cell dysfunction to account for the higher prevalence of abnormal FLC ratio observed among these older individuals.

The Mayo Clinic has reported that a skewed FLC ratio is a significant predictor of progression to MM but that risk of progression to MM is stable over time and unrelated to age at diagnosis of MGUS [10]. The Spanish PETHEMA group, by contrast, has previously shown that the presence of immunoparesis is significantly associated with progression from smoldering MM to MM and is a borderline significant risk factor in MGUS [9]. In this study, we show that advancing age is linked to immune changes represented by waxing and waning frequency of immunoparesis in a population of older individuals, but that prevalence of MGUS increases with advancing age. Clinical management strategies based on the predictive models inform patient counseling and follow-up, and additional investigations are needed to better characterize the role of immunoparesis as a risk factor for transformation to MM in relation to age.

Conclusions

In summary, in this population of older people, we found a striking disassociation between prevalence patterns of MGUS and impaired immunoglobulin production, suggesting that separate mechanisms are involved in the development of MGUS and immunoparesis in advanced age. Compared to the previous studies of younger MGUS patients, we found older MGUS patients to have a substantially higher prevalence of abnormal FLC ratio (33 vs. 50%, respectively). Given that immunoparesis and a skewed FLC ratio are included in current clinical risk models to predict transformation from myeloma precursor states to MM [9,10], our findings further emphasize the need for molecularly and genetically defined predictors of progression [25].

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