

Patterns of monoclonal immunoglobulins and serum free light chains are significantly different in black compared to white monoclonal gammopathy of undetermined significance (MGUS) patients

Brendan M. Weiss,^{1*} Alex Minter,¹ Jude Abadie,² Robin Howard,³ Joao Ascencio,⁴ Geraldine P. Schechter,⁴ Michael Kuehl,⁵ and Ola Landgren⁶

Monoclonal gammopathy of undetermined significance (MGUS), the precursor to multiple myeloma, is more common in blacks than whites. The serum free light chain (sFLC) assay is an important prognostic test in MGUS, but no study has evaluated sFLC levels and ratios in black MGUS patients. One-hundred and twenty-five black MGUS patients at two urban centers were compared to the white population of the Mayo Clinic. The median age for blacks was 73 years [41–94] and 75% were male. The M-protein isotype in blacks was 81% IgG, 13% IgA, 2% IgM, and 4% biclonal compared to 70%, 12%, 16%, and 2%, respectively, in whites, ($P < 0.0005$). The median M-protein concentration for blacks was 0.44 gm/dL (trace–2.33) compared to 1.2 gm/dL in whites. An abnormal sFLC ratio was present in 45% of black compared to 33% of white ($P = 0.01$) patients. Using the Mayo Clinic risk model, black patients had a significantly lower proportion of higher risk MGUS compared to whites: low 43%, low-intermediate 45%, high-intermediate 10%, and high 2% ($P = 0.014$). Black patients with MGUS have significantly different laboratory findings compared to whites. The biologic basis for these disparities and their effect on prognostic assessment is unknown. Prognostic models based on these biomarkers should be used cautiously in nonwhite populations. *Am. J. Hematol.* 86:475–478, 2011. © 2011 Wiley-Liss, Inc.

Introduction

Monoclonal gammopathy of undetermined significance (MGUS) is a common premalignant condition affecting at least 3% of those over the age of 50 years [1]. It is characterized by the presence of a monoclonal immunoglobulin (M-protein) without evidence of multiple myeloma (MM) or a related lymphoproliferative malignancy [2]. It has recently been shown that MGUS precedes nearly all cases of MM [3,4]. However, it is important to realize that most patients with MGUS do not develop a lymphoproliferative malignancy [5]. Given that MGUS is one of the most common premalignant conditions known, it is of considerable importance to understand clinical and biological factors that increase the risk of progression. This will lead to improved patient counseling and the development of optimal strategies for monitoring, which currently are mostly based only on observational studies and expert opinions [6,7].

Both MGUS and MM display striking racial disparities, with both conditions being greater than twofold more common in African-Americans and Africans compared to whites [8–10]. Prior studies have noted distinct differences in blacks with MGUS compared to whites, including lower levels of M-protein, younger average age distribution, and a lower prevalence of IgM gammopathy [9,11–14]. In an analysis of over 30,000 patients with MM in the Surveillance, Epidemiology and End Results registries, black patients with MM had a better survival, suggesting that black MM patients may have a more indolent tumor biology compared to whites [10].

Despite these clinical, laboratory, and biologic differences, the rate of transformation of MGUS to MM appears to be similar between the races [8]. The identification of high-risk features for transformation from MGUS to MM has been derived from predominantly white populations, raising the question whether these biomarkers are applicable to other populations [5,15,16]. The serum free light chain (sFLC) assay is a novel test that is now recommended for the evaluation of all patients with a monoclonal gammopathy [17]. The sFLC assay can detect free kappa and free lambda light chains in serum. An abnormal kappa:lambda ratio indicates the presence of a monoclonal plasma cell population.

The prevalence of abnormal kappa:lambda ratios is lower in MGUS (30–40%), [15,18] than in smoldering MM (90%), [19] and MM (95%), [20], suggesting that excess monoclonal light chains indicate clonal evolution toward a malignant phenotype. In the setting of MGUS, the presence of an abnormal sFLC ratio is associated with a 2.6-fold higher risk of transformation to MM compared to patients with a normal ratio [15]. Based on white individuals from Minnesota, the Mayo Clinic has developed a risk stratification model for the progression of MGUS to MM that incorporates three adverse risk factors: an abnormal sFLC ratio, non-IgG immunoglobulin isotype, and M-protein concentration greater than 1.5 gm/dL. Patients are considered low-risk if there is an absence of all factors, any one factor is low-intermediate

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¹Hematology-Oncology, Brooke Army Medical Center, San Antonio, Texas;

²Pathology and Area Laboratory Services, Brooke Army Medical Center, San Antonio, Texas; ³Clinical Investigation, Walter Reed Army Medical Center, Washington, District of Columbia; ⁴Hematology Section, Washington Veterans Affairs Medical Center and George Washington University, Washington, District of Columbia; ⁵Genetics Branch, National Cancer Institute, National Institutes of Health; ⁶Medical Oncology Branch, National Cancer Institute, National Institutes of Health

*Correspondence to: Brendan M. Weiss, Hematology-Oncology Service, Walter Reed Army Medical Center, 6900 Georgia Avenue, NW, Washington, DC 20307. E-mail: brendan.weiss@us.army.mil

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risk, any two factors is high-intermediate risk, and all three factors are considered high risk. The absolute risk of progression to MM at 20 years for each group is 5, 21, 37, and 58%, respectively.

Given the aforementioned racial disparity patterns for plasma cell dyscrasias and the importance of the sFLC ratio in prognostic assessment of MGUS, we have performed the first systematic evaluation of the sFLC assay in black patients with MGUS and compared them to the predominantly white patients of the Mayo Clinic population [15].

Methods

All black MGUS patients referred to the Hematology Clinics at Walter Reed Army Medical Center (WRAMC) and the Washington Veterans Affairs Medical Center (VA) were eligible. The institutional review boards at both institutions approved the study. Patients at WRAMC were enrolled in a retrospective chart review covering the years 2005–2008, as the sFLC was performed routinely in MGUS patients referred to the Hematology Clinic. Patients at the VA were enrolled in a prospective trial between 2008 and 2010, and the sFLC assay was performed at WRAMC. sFLC levels were determined by automated immunoturbidometric assays for free κ (normal range, 3.3–9.4 mg/L) and free λ (normal range 5.7–26.3 mg/L) on a Bayer Advia 1650 (Bayer Diagnostics, Tarrytown, NY) using commercial reagents (Freelite, The Binding Site, Birmingham, UK). The κ/λ ratio was calculated (normal range, 0.26–1.65). The reference ranges used were those established by Katzmann et al. [21] at the Mayo Clinic. All patients were categorized for their risk of progression using the Mayo Clinic model (see Introduction section) [15]. The clinical features and risk groups were compared to the predominantly white Mayo Clinic population by the Fisher's exact test.

Results

The characteristics of the patients are shown in Table I. The median age was 73 years (range, 41–94), and 75% were male, which in comparison with the white population

trended toward slightly older ($P = 0.054$) and significantly more males ($P < 0.0005$). The immunoglobulin isotype was 81% IgG, 13% IgA, 2% IgM, and 4% biclonal compared to 70% IgG, 12% IgA, 16% IgM, and 2% biclonal in the white population ($P < 0.0005$; see Fig. 1). Black MGUS patients had significantly lower M-protein concentrations compared to the white population ($P < 0.0005$; Fig. 2). The median M-protein concentration in black patients was 0.44 gm/dL compared to 1.2 gm/dL in white patients. An abnormal sFLC ratio was seen in 45% of patients compared 34% of white patients ($P = 0.01$). When categorizing black patients by the Mayo Clinic model, there was a lower frequency of high-risk MGUS groups in the black population compared to the white population ($P = 0.014$; Fig. 3).

Discussion

To our knowledge, we have performed the first systematic evaluation of the sFLC assay in a nonwhite MGUS population. We have demonstrated that black MGUS patients have a higher frequency of abnormal sFLC ratios compared to whites. In addition, we have confirmed the results of other studies that blacks have less frequent IgM MGUS and lower concentrations of M-protein than whites. A consequence of these results is that fewer black MGUS patients have high-intermediate or high-risk MGUS based on the Mayo Clinic model, which includes all these factors. Therefore, this model may not be suitable to accurately assess prognosis in black MGUS patients, raising the question: how can this model be improved to be applicable across an ethnically diverse population of MGUS patients?

First, a risk stratification model for progression to MM in patients with non-IgM MGUS should be developed separately from patients with IgM MGUS. It is important to consider IgM MGUS a distinct entity based on clinical and biological features [22]. IgM MGUS arises from postgerminal center lymphoid or lymphoplasmacytoid cells that have undergone somatic hypermutation but have not undergone isotype switching [23]. In most instances, IgM MGUS is a precursor to Waldenstrom's macroglobulinemia (WM), chronic lymphocytic leukemia (CLL), and non-Hodgkin's lymphoma (NHL) [22]. The gene expression profile of WM is distinct from MM [24]. Although rare cases of IgM MM have been reported, it appears that the absence of t(11;14), a common finding in MM, allows a distinction between these entities [25]. Our finding that IgM MGUS has a low frequency in blacks is consistent with other studies [9,11] and is also consistent with the lower frequency of WM, [26,27] B-cell NHL [28] and CLL [29] in blacks.

TABLE I. Characteristics of the Patients

	Blacks 125	Whites 1148	<i>P</i>
Total, <i>n</i>			
Age, median (years)	73 (41–94)	72	
Age, categories, <i>n</i> (%)			
0–49	4 (3)	66 (6)	0.054
50–59	22 (18)	123 (11)	
60–69	23 (18)	286 (25)	
70+	76 (61)	673 (59)	
Gender, male, <i>n</i> (%)	94 (75)	622 (54)	<0.0005
Immunoglobulin heavy chain isotype, <i>n</i> (%)			
IgG	101 (81)	806 (70)	<0.0005
IgA	16 (13)	135 (12)	
IgM	3 (2)	182 (16)	
Biclonal	5 (4)	25 (2)	
Abnormal sFLC ratio, <i>n</i> (%)	56 (45)	372 (33)	0.01

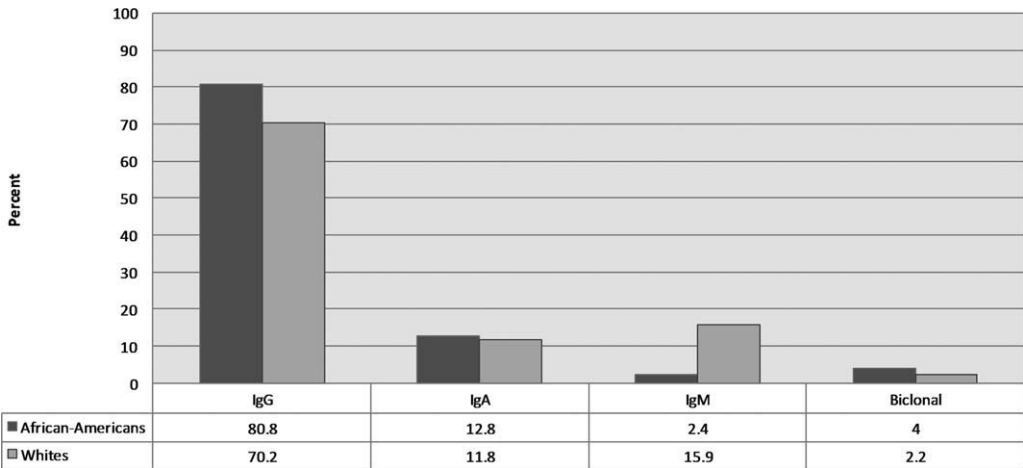


Figure 1. Comparison of monoclonal immunoglobulin isotypes between blacks and whites, $P < 0.0005$.

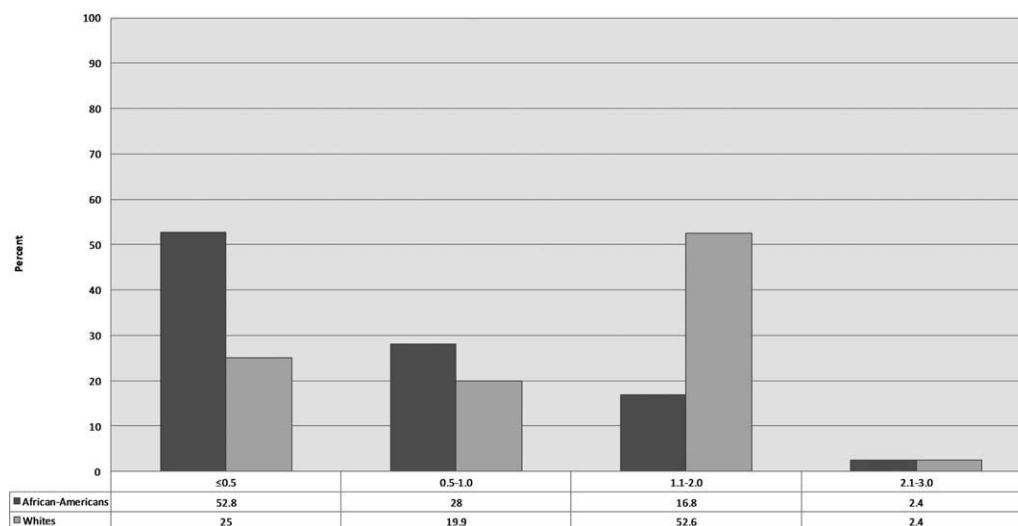


Figure 2. Comparison of M-protein concentrations between blacks and whites, %, $P < 0.0005$.

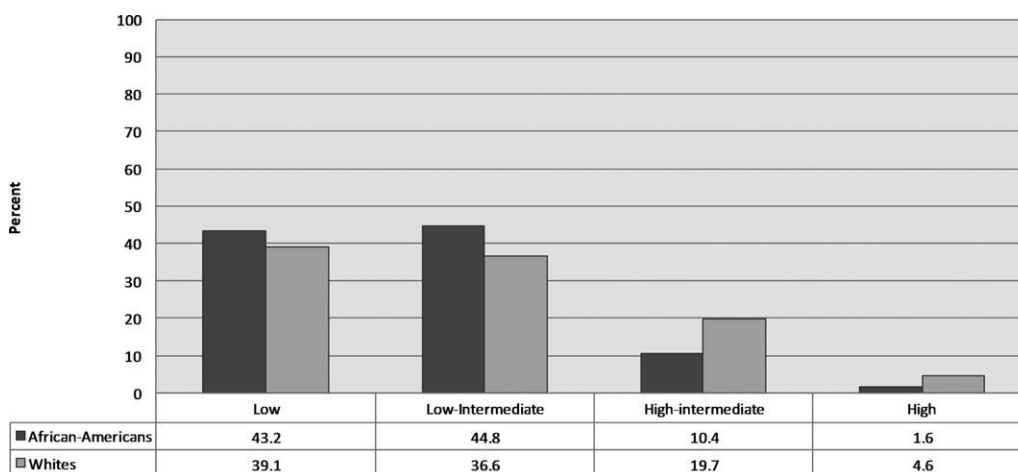


Figure 3. Comparison of Mayo Clinic Risk Groups between blacks and whites, $P = 0.014$.

Second, we demonstrated a lower level of M-protein in our study, which is consistent across other studies of blacks with MGUS. For example, in a study of elderly patients in the United States, 40% of blacks with MGUS had an M-protein concentration <0.5 g/dL, which is similar to our study [11]. The majority (76%) of MGUS patients in Ghana had an unquantifiable concentration of M-protein compared to 12% [9]. It remains unclear why this disparity exists, although a potential explanation is differences in the response to antigenic stimulation between the races. Interestingly, higher levels of polyclonal immunoglobulins are present in those of African descent [30–32]. These findings persist with migration, suggesting that germline genetic differences may be causative [33,34]. Various immune-mediated conditions, including autoimmune and infectious conditions, are associated with the development of MGUS and MM as well as NHL [35,36]. Given that there are several shared mechanisms of uncontrolled lymphoproliferation occurring in autoimmune disease and B-cell malignancies [37,38], it is possible that this contributes to our findings.

Third, there is a marked disparity in sFLC ratios in blacks compared to whites in our study. The reasons for this disparity are unknown. sFLC levels are dependent on plasma cell production of free light chains and renal clearance. As suggested earlier, there may be genetic differences in light chain production. Chronic kidney disease also

has a striking racial disparity, with high rates in black populations, which may have affected our results [39]. sFLC ratios increase with declining renal function, and an alternative reference range of 0.26–3.1 has been suggested in this setting [40]. Also, in this study, patients with polyclonal hypergammaglobulinemia [31,32], as occurs in significantly more black than white patients, also exhibited sFLC ratios up to 3.1. The reference range used in this and other studies was based on data from the predominantly white Mayo Clinic population. Therefore, a study evaluating sFLC levels in a black population to establish appropriate reference ranges should be considered.

Other biomarkers associated with progression of MGUS to MM should be explored in ethnically diverse populations. A currently available alternative approach is flow cytometry of bone marrow plasma cells. The Spanish have demonstrated that the identification of a high proportion of aberrant plasma cells based on immunophenotypic markers and aneuploidy are adverse risk factors for progression from MGUS to MM [16]. Although this study was also performed in an ethnically homogenous population, it is possible that these factors are less subject to racial disparity. A major limitation of this approach is its invasiveness, expense, and need for technical expertise in flow cytometry of plasma cells. In the future, other approaches may be available. Novel imaging modalities that evaluate important physiologic processes in the pathoge-

nesis of MGUS to MM, such as angiogenesis and bone destruction, can be imaged by dynamic contrast enhanced magnetic resonance imaging and 18-fluoride positron emission tomography, respectively, and may prove useful in prognosis [41,42]. Molecular markers, such as gene expression profiling and microRNA profiles, are also promising in plasma cell dyscrasias [43,44].

A major strength of our study is that all assays were done in a central laboratory. Our study has a few limitations. First, we do not have data on rates of progression to MM. Second, this study was performed at institutions that serve predominantly active and retired military personnel and veterans, resulting in an overwhelming male population. Third, the patient population was drawn from referrals to a subspecialty clinic in universal access health care systems. Thus, comparisons to the aforementioned studies in this area, which drew on general medical populations, should be made cautiously. These results need to be replicated in a larger, ethnically diverse population, ideally with data on the rate of progression to MM.

In conclusion, this study demonstrates that serum protein abnormalities, including sFLC, are significantly different in blacks and whites. We propose that future research is needed to better define the reference ranges for sFLC in blacks. Recent literature suggests a risk-adapted approach to management of MGUS using the three factors in the Mayo Clinic model [6,7]. However, using these biomarkers in a black population may exclude a significant proportion of patients from receiving optimal follow-up. The Spanish model may be a reasonable alternative approach for prognosis in MGUS. Until further studies are performed to establish optimal biomarkers for progression in nonwhite populations with MGUS, using such a risk-adapted approach may not be prudent.

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