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Monoclonal Gammopathy of Undetermined Significance: Genetic vs Environmental Etiologies

Since its first description in 1978,[1] monoclonal gammopathy of undetermined significance (MGUS) has remained an enigmatic clinical entity as a precursor to development of multiple myeloma (MM). Its progression to MM occurs at a constant rate of 1% per year, and the rate does not change with time. In most patients, MGUS does not progress to MM, requiring no therapeutic intervention. Presence of non-IgG M protein, serum M component greater than 1.5 g/dL, and an abnormal free light chain ratio predicts progression of MGUS to MM.[2] However, factors predisposing to the development of MGUS are as yet unidentified.

A number of cytogenetic and molecular changes observed in MM are also observed in MGUS. For example, the 14q32 (IgH) translocation observed in MM was also observed in 46% of patients with MGUS in 2 different studies.[3,4] In 1 of these studies, t(11;14)(q13;q32) was observed in 25%, t(4;14)(p16;q32) in 9%, and t(14;16)(q32;q23) in 5%, with consequent dysregulation of the cyclin D1, *FGFR3*/*MMSET*, and *C-MAF* genes involved in these translocations, respectively.[4] These data suggest a possible role of these genetic changes in the development of MGUS. Similarly, chromosome 13 deletion, considered a poor prognostic feature in MM, is also observed in MGUS; however, its association with progression to MM is unclear.[5] Expression profile studies have further identified the molecular signature of MGUS, which could help identify the role of aberrant gene expression in the initiation of the MGUS clone and the multistep process involved in its progression to MM.[6]

Although the molecular changes associated with MGUS have been described, the etiological factors predisposing to the development of MGUS remain under investigation. Differences in the prevalence of MGUS in various ethnic populations have provided clues to the origin of the disease, both its genetic predisposition and environmental factors that could modulate development of MGUS. The studies by Landgren et al[7] and Iwanaga et al,[8] published in this issue of *Mayo Clinic Proceedings*, provide interesting and important evidence in 2 ethnically very diverse patient populations.

The study by Landgren et al evaluates the prevalence of MGUS in an adult male population in Ghana and compares it with MGUS prevalence in a white population in the United States. Their results confirm a 2-fold increase in prevalence of MGUS in the Ghanaian population vs the white population from Minnesota.[9] A similar increase was observed in the African American vs white population in the United States, raising the question of common causes, whether genetic or environmental, that could be responsible for higher prevalence in people of African origin. This is a unique study that for the first time investigates the prevalence of MGUS in an African country in a large patient population. The results are interpreted as supporting the hypothesis of a race-related genetic susceptibility that predisposes African Americans to higher rates of MGUS. However, it is important to note that the similarly increased prevalence in the Ghanaian and African American populations does not necessarily confirm a genetic basis for the higher prevalence; it could also be related to exposure to similar environmental factors.

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Extensive information regarding various infections acquired by the study participants in Ghana has not shown a correlation between history of infectious disease and the development of MGUS. Chronic infections and autoimmune diseases have been reported to be associated with higher frequency in MGUS as well as MM. For example, Malik et al[10] reported that 39 (66%) of 59 patients with MGUS had *Helicobacter pylori* infection; when treated, 11

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TABLE 1. **Prevalence of Monoclonal Gammopathy of Undetermined Significance in Large Studies From Different Countries Across the Globe**

Study population	No. of participants	Age (y)	Prevalence (%)
Ghana[7]	917	50-74	5.84
Olmsted County, MN[16]	21,463	≥50	3.2
Provincial Hospital, Italy[17]	35,005	11-75	2.9
Nagasaki City, Japan[8]	52,802	44-70	2.4
Finistere, France[18]	30,279	≥50	1.7
New York, NY[19]	73,630	—	1.2
Sweden (South)[20]	6995	≥25	0.9
Rangiora, New Zealand[21]	2,192	>21	0.7
General Hospital, Italy[22]	102,000	—	0.7

of the 39 patients had reduction or resolution of their chromatographic M-protein spike.[10] In contrast, a serological study in a smaller cohort of patients from Olmsted County did not identify a higher incidence of *H pylori* infection in patients with MGUS.[11] Detailed investigations might be required to identify environmental factors that could explain the higher prevalence of MGUS in Ghana.

Unlike the US population (both white and African American), no significant variation by age group was observed in the Ghanaian population. This lack of increase in prevalence of MGUS with age is intriguing. In the white population from Olmsted County, the prevalence of MGUS increased from 1.83% in those aged 50 to 54 years to 5.12% in those aged 70 to 74 years.[9] A similar increase in prevalence has been reported previously in the African American population.[12] However, in the Ghanaian population, the prevalence was stable in those aged 50 to 74 years (5.33% in those 50-54 years and 5.38% in those 70-74 years), suggesting that some differences exist between the 2 populations. It is difficult to attribute this stable rate in the Ghanaian population to a single cause, but if genetic background is considered to be similar between the African American and Ghanaian populations, then the high prevalence at an earlier age in Ghanaians might reflect the role of environmental factors in the development of MGUS. In a study in an elderly population in the United States, the increased prevalence in African Americans could not be explained by socioeconomic conditions, household size, or family income.[13] However, an age-related increase in prevalence was observed in this population. Similarly, no statistical variation with ethnicity, educational status, or history of infections was observed in the Ghanaian population. Although this study was limited to men, comparison with the US male population provides a similar reference point for assessment.

The study by Iwanaga et al investigates the prevalence of MGUS in 52,802 atomic bomb survivors in Nagasaki City, Japan. In this Japanese population, the prevalence in those older than 50 years was 2.4%, a substantially lower rate than the observed prevalence of 3.2% in a population of similar age from Olmsted County. This large study confirms the previously reported findings of a lower prevalence of MGUS in an Asian population than in Western countries.[14] However, in the Japanese population, as in the white population, an age-related increase in prevalence and a higher prevalence in men than women (2.8% vs 1.6%; $P<.001$) were observed, suggesting that a similar pathogenetic mechanism could be operative in these ethnically diverse populations. The prevalence reported by Landgren et al in the Ghanaian population was substantially higher (5.8%). The study by Iwanaga et al is also interesting in that it evaluated atomic bomb survivors in Nagasaki City. It is interesting that radiation exposure did not lead to higher prevalence of MGUS. Although the dose of radiation in this population was considered small, this study provides a future opportunity to study the effect of low-dose radiation on development of MGUS by considering the study participants' distance from the hypocenter of the nuclear explosion. The large number of study participants and very long follow-up period from exposure provide a unique opportunity for further investigation.

A number of physical, environmental, and chemical factors such as exposure to asbestos, fertilizer, mineral oils, pesticides, and radiation have been implicated in the development of MGUS and MM.[15] Similarly, frequent or chronic infections and autoimmune diseases have been associated with development of MGUS. Do the studies by Landgren et al and Iwanaga et al suggest that MGUS is related to genetic risk or exposures to different infections, autoimmune diseases, chemicals, diets, or unique environmental factors? The complex differences and patterns of prevalence of MGUS in ethnically diverse populations (Table 1) provide insight into the pathogenesis of the disease. In addition to possible genetic links associated with ethnic background, a number of cultural and regional factors could lead to exposure to some of the risk factors contributing to the observed differences in prevalence.

The type of immunoglobulins observed in these studies differed. Although all studies have reported a higher frequency of IgG, the frequency of IgM MGUS differed by population: Ghanaian, 5.6%; Japanese, 7.5%; Olmsted County, 17%[16]; French, 24%[18]; and Swedish, 8%.[20] Although the biological or epidemiological explanation for these ethnicity-related differences remains unclear, such differences point to factors other than genetic differences. It is interesting to note that the incidence of Waldenström macroglobulinemia in the white population is twice that in the African American population in the United States.[23]

In summary, these studies confirm ethnic differences in the prevalence of MGUS; identify a similar prevalence of

MGUS in patients from Africa and Americans of African descent, raising questions about genetic factors that predispose to the development of MGUS; and highlight differences such as lack of age-related increase in prevalence. Two important observations that require further investigation from the study by Landgren et al are the higher incidence of MGUS at an earlier age in a Ghanaian population and the significantly higher proportion of patients with undetectable, immunofixation-positive only M protein (75.9% vs 13.1% in Olmsted County). Does the latter finding reflect a more sensitive detection method, a direct association with frequent infections, or a different subtype of MGUS with a different long-term outlook? The studies by Landgren et al and Iwanaga et al also provide opportunities to identify and study preventive strategies (especially in groups with high prevalence), targeting possible risk factors, if identified.

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