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The significance of monoclonal gammopathy of undetermined significance

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Monoclonal gammopathy of undetermined significance (MGUS) is characterized by a serum M protein concentration of less than 30 g/L, fewer than 10% clonal plasma cells in the bone marrow, and the absence of end-organ damage that can be attributed to the plasma cell proliferative disorder. End-organ damage is defined by hypercalcemia, renal insufficiency, anemia, or bone lesions (CRAB) related to the plasma cell proliferative disease.[1]

The prevalence of MGUS was 3.2% in 21,463 predominantly white residents of Olmsted County, Minnesota, who were 50 years of age or older.[2] The prevalence was 4.0% in men and 2.7% in women, 5.3% in persons 70 years of age or older, and almost 9% in men older than 85 years of age. Despite the common occurrence of MGUS, it is markedly underdiagnosed in the general population because this condition is asymptomatic and does not produce the signs or symptoms of multiple myeloma or related disorders. We found that the prevalence of MGUS in Olmsted County was 3.8% in persons 70 years of age, but that the prevalence of clinically detected cases at this age was only 0.8%. Thus, only 21% of patients with MGUS at the age of 70 were detected by clinical practice in Olmsted County.[3] In contrast, at the age of 80, 33% of patients with MGUS were detected by routine clinical practice, while the clinical detection rate was only 8% in those 50 years old. Overall, only 22% of patients with a known MGUS were recognized by routine clinical practice in Olmsted County, Minnesota.

The prevalence of MGUS in African Americans[4,5] and Africans[6] is approximately double that in whites. The prevalence in Japan is lower than in whites.[7]

The cause of MGUS is not known. In a report of atomic bomb survivors, those exposed to high levels of radiation at a young age had an increased risk of MGUS. Pesticides have also been implicated. In a study of pesticide applicators living in Iowa or North Carolina, the age-adjusted prevalence of MGUS was 1.9-fold higher than in men from Minnesota.[8] A 3-fold or greater risk was found in users of dieldrin, a chlorinated insecticide and the carbon-tetrachloride-carbon disulfide fumigant mixture. There was also an increased risk of MGUS in those exposed to the fungicide chlorthalonil. There is also a genetic element. A report on 247 first-degree relatives of 97 MGUS patients showed an approximate 2-fold higher risk of MGUS in first-degree relatives.[9]

What is the importance of MGUS? Is it simply an interesting laboratory finding or is it of importance to the patient? Prior to 1978, the presence of an asymptomatic M protein was often referred to as *benign monoclonal gammopathy*. In that year, we published the findings of a study of 241 patients with a monoclonal gammopathy but no evidence of multiple myeloma, Waldenström's

macroglobulinemia, AL amyloidosis or a lymphoproliferative disorder. In our study, we coined the term *monoclonal gammopathy of undetermined significance* (MGUS) to describe such patients because multiple myeloma or a closely related plasma cell disorder developed at a rate of 1.5% per year, indicating that the condition was not entirely benign.[10] This cohort was followed up for 3,579 person-years of observation. Sixty-four patients (27%) developed multiple myeloma or a related disorder. The interval from the recognition of MGUS to diagnosis of multiple myeloma or a related disorder ranged from 1 to 32 years (median 10.4 years). The risk of progression, which was 1.5% per year, was still continuing without change after 25 years of observation.[11]

In order to confirm the findings of the 241 Mayo Clinic patients from the USA and other countries which may be subject to referral bias, we conducted a study of 1,384 patients with MGUS from the 11 counties of Southeastern Minnesota evaluated at the Mayo Clinic from 1960 to 1994.[12] The median age at diagnosis was 72 years, which is 8 years older than that of the original cohort of 241 patients. During a follow-up of 11,009 person-years (median 15.4 years; range, 0 to 35 years), 70% died, indicating a mature follow-up. Multiple myeloma, AL amyloidosis, lymphoma with an IgM serum protein, Waldenström's macroglobulinemia, plasmacytoma or chronic lymphocytic leukemia developed in 115 patients (8%). The cumulative probability of progression was 10% at 10 years, 21% at 20 years, and 26% at 25 years. Thus, the risk of progression was approximately 1% per year. These patients were at risk of progression, even after more than 25 years of follow-up. The number of patients with progression to a plasma cell disorder (n=115) was 7.3 times the number expected. The risk of developing multiple myeloma was increased 25-fold, that of developing Waldenström's macroglobulinemia 46-fold, and that of AL amyloidosis 8.4-fold. The risk of lymphoma was moderately increased at 2.4-fold, but this risk was underestimated because only lymphomas associated with an IgM protein were counted in the observed number, while the incidence rates for lymphomas associated with IgG, IgA, and IgM proteins were used to calculate the expected number. Multiple myeloma accounted for 75 of the 115 cases (65%) of progression to a malignant plasma cell disorder. The characteristics of these 75 patients who developed multiple myeloma following the presence of MGUS were comparable with those of the 1,027 patients with newly-diagnosed multiple myeloma who were referred to the Mayo Clinic between 1985 and 1988, except that the Southeastern Minnesota population was older (median 72 years *vs.* 66 years) and the percentage of men was lower (45% *vs.* 60%).[13] This study confirmed that MGUS is indeed an important disorder, in which the risk of progression to malignancy persists indefinitely.

The finding that MGUS predisposes to multiple myeloma raises the question of whether multiple myeloma is always preceded by a MGUS or whether the disease can arise *de novo*. In clinical practice, data from the Mayo Clinic series of 1,027 consecutive patients with multiple myeloma suggest that only 20% of these patients had a known prior diagnosis of MGUS. We had the opportunity of utilizing the USA PLCO (prostate, lung, colorectal, and ovarian) Cancer Screening Trial to address this question. In this study of 77,469 people who were cancer-free, we identified 71 individuals who subsequently developed multiple myeloma during the study in which serially collected serum samples were obtained from 2 years to 9.8 years prior to the diagnosis of the myeloma. The median age of these 71 patients was 70 years and 71.4% were male. MGUS was present in 100% of patients 2 years prior to the diagnosis of multiple myeloma. At 5 years prior to the diagnosis of multiple myeloma, 95% had MGUS while at 8 or more years prior to the diagnosis of multiple myeloma, 82.4% had a preceding MGUS.[14] The median size of the M protein increased from 0.9 g/dL at 8+ years to 1.6 g/dL at 2 years prior to the diagnosis of multiple myeloma. Approximately one-half of the myeloma patients had a year-by-year increase in M pro-

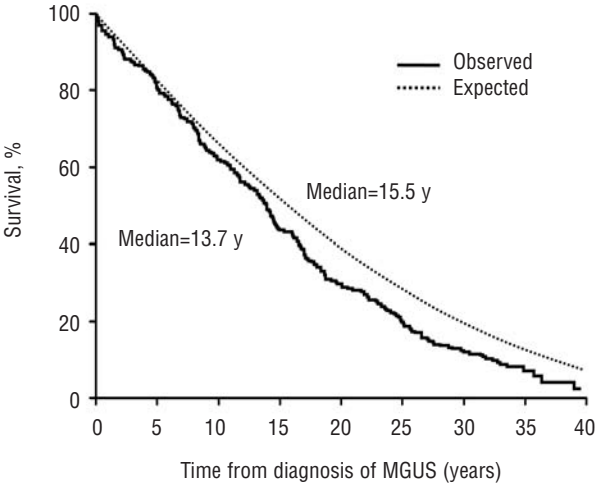

Figure 1. **Survival rate of 241 patients with monoclonal gammopathy of undetermined significance compared with expected survival rate of the USA population using 1930-2000 decennial life tables. Reproduced from Kyle *et al.*[11]**

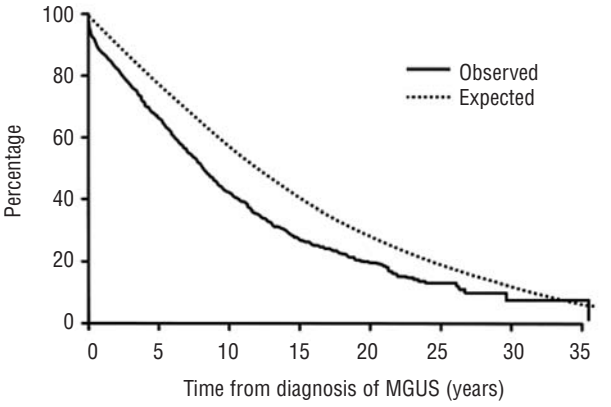

Figure 2. **Survival of 1384 patients with monoclonal gammopathy of undetermined significance from South-Eastern Minnesota compared with a normal population (8.1 *vs.* 11.8 years, respectively) ($p<0.001$). Reproduced from Kyle *et al.*[17]**

tein until the diagnosis of multiple myeloma. The type of M protein was IgG (68%), IgA (21.5%), IgM (1.5%), or biclonal (3%), and 4.7% had light chain MGUS. Thus, this study established that virtually all patients with multiple myeloma have a preceding MGUS. These findings were confirmed by another study in which 27 of 30 patients with multiple myeloma had a preceding monoclonal protein. Three patients had no evidence of an M protein; one had only one prediagnostic sample available 9.5 years before the diagnosis of multiple myeloma, while the other two patients had IgD myeloma and their most recent prediagnostic samples were 5.3 and 3.3 years prior to the diagnosis of myeloma.[15]

In this issue of the journal, Kristinsson and colleagues describe an important study determining the mortality patterns and causes of death in MGUS patients in comparison to controls.[16] They identified a nation-wide cohort of 4,259 MGUS patients diagnosed from 1986 to 2005 and compared them to 16,151 matched controls. They demonstrated excess mortality in patients with MGUS. The excess mortality increased with longer follow-up. Younger patients with MGUS had a significantly lower excess mortality rate compared to that of older patients. MGUS patients had an increased risk of dying from multiple myeloma, Waldenström's macroglobulinemia, other lymphoproliferative malignancies, other hematologic malignancies, amyloidosis, bacterial infections, ischemic heart disease, other heart disease, other hematologic conditions, liver disease, and renal disease. The major shortcoming of this study is that since MGUS was diagnosed clinically, the causes of death besides plasma cell disorders are likely affected by the reason the patient underwent electrophoresis rather than the presence or absence of MGUS detected on that test. This bias can be overcome only if a study is undertaken on a population-wide basis, or if the deaths in patients who were tested and found negative for MGUS can be used as the control group.

Nevertheless, we have also found a shorter survival in MGUS patients when compared to the age- and sex-matched normal population. In our report of 241 patients with MGUS, the median survival was 13.7 years, compared to 15.5 years for the USA population using 1930 to 2000 decennial life tables (Figure 1). Each patient was matched to the control population by age, sex, and date of entry.[11] The median survival of our 1,384 patients from Southeastern Minnesota was 8.1 years, compared to the 11.8 years expected for Minnesota residents of matched age and sex[17] (Figure 2). Van de Poel *et al*. reported that the long-term survival of 334 patients with MGUS was slightly shorter than the expected survival of age- and sex-adjusted controls.[18] Survival of patients with MGUS has also been reported in cohorts from the Netherlands[19] and from Denmark.[20] Kristinsson *et al.* have confirmed these findings in their article in this issue of the journal and have extended this work by comparing the causes of death with those of the matched controls.[16]

The goal of our overall efforts is to identify patients with MGUS who are at the highest risk of progression to multiple myeloma or another disorder. The next step is to treat these MGUS patients in an effort to reduce or prevent the development of multiple myeloma. Demonstration of a treatment capable of delaying or preventing progression requires a controlled clinical trial with a placebo comparator arm which shows a low toxicity profile, no impact on quality of life, and an improvement in overall survival. The use of current agents outside the context of clinical trials is not recommended because of the unknown ratio between potential benefit and toxicity. At present, no current agents are recommended for clinical use in MGUS.[21]

The *benign monoclonal gammopathy* patient of the past has been shown to be an important element in unlocking the mysteries of the plasma cell dyscrasias – particularly multiple myeloma. It is well accepted that MGUS patients have an excess risk of developing multiple myeloma and related plasma cell disorders. It has recently been demonstrated that virtually all patients with multiple myeloma have a preceding MGUS.[14,15]

We first need to try and understand the etiology and biology of MGUS better. Why do blacks have a higher risk of progression than whites? Is the reason for the racial disparity genetic or environmental? What other factors may play a role? It is apparent that genetic factors may predispose patients to develop MGUS and ultimately multiple myeloma or a related disorder. For example, Vachon *et al*. demonstrated a 2-fold greater risk of MGUS in first-degree relatives of MGUS patients when compared with the control population.[9] We now need to try and identify specific genes that may be involved in familial predisposition to developing MGUS. Environmental risk factors also need to be studied. It has been shown that exposure to radiation at an early age results in an increased frequency of MGUS [7] and that farmers and agricultural workers also have an elevated risk of multiple myeloma.[22] Insecticides, herbicides, and fungicides have all been hypothesized as potential causes in this population. It has also recently been reported that a cohort of males exposed to insecticides from North Carolina and Iowa have a 2-fold increased rate of MGUS when compared to an age-adjusted population from Southeastern Minnesota.

Second, there are likely many different cytogenetic categories of MGUS that need to be studied in detail, to determine, for instance, whether progression to myeloma is more rapid in those with translocations such as t(4;14).

The fact that all patients with multiple myeloma have a preceding MGUS makes it imperative that we identify potential risk factors responsible for the progression of MGUS to a serious plasma cell dyscrasia. Since only a small number of patients with MGUS progress on an annual basis, the number of subjects needed for a preventive strategy is large. Preventive studies therefore need to target those at the highest risk of progression. Definitive studies to prevent progression in high-risk patients will be feasible in the future, but since MGUS is asymptomatic, safety is an important issue in these trials. We believe that demonstration of a treatment capable of delaying progression requires a controlled clinical trial with a placebo comparator arm and such a trial must show that the treatment improves overall survival, preserves quality of life, and has a low toxicity. Treatment of

MGUS outside the context of a clinical trial is not recommended because of the uncertain ratio between potential benefit and toxicity. Future studies should refine the risk factors for progression and develop criteria to identify people at high risk of progression who are candidates for preventive trials, as well as identify patients without any risk of progression who can be reassured.

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Granulocyte transfusion therapy: randomization after all?

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Severe neutropenia remains an important and serious complication of cancer chemotherapy and hematopoietic stem cell transplantation. A relation between the degree and duration of neutropenia and the risk of infections has been observed since the 1960's.[1] As the use of chemotherapy for the treatment of malignancy increased, the incidence of neutropenia and severe infections increased as well. The strongest predictor of recovery from infections is recovery of neutrophil production by the marrow and an adequate number of blood and tissue neutrophils.[2] This led to the concept of granulocyte replacement by transfusion therapy as a possible way to bridge the gap between marrow suppression and neutrophil recovery.