K. Kyle coined the term “monoclonal gammopathy of undetermined significance” (MGUS) for a condition that consists of a serum M-protein lower than 3 g/dL and less than 10% bone marrow plasma cells (BMPCs) in the absence of clinical manifestations due to the monoclonal gammopathy.1 What we know about MGUS is (1) a high prevalence of 3.2% and 5.3% in persons older than 50 and 70 years, respectively, (2) the plasma cell clone has genetic and phenotypic profiles similar to myelomatous plasma cells, and (3) the average transformation rate to a malignant plasma cell disorder is 1% to 1.5% per year with actuarial probabilities of progression at 10 years of follow-up ranging from 12% to 17% and at 20 years from 25% to 34%. We also know that the factors associated with a higher risk of MGUS progression are M-protein concentration, proportion of BMPCs, IgA isotype, abnormal immunoglobulin free light chain (FLC) ratio, ratio between phenotypically aberrant and normal BMPC, and evolution pattern: “evolving” versus “nonevolving.”2-6 However, there are a number of unknown questions concerning MGUS and its relationship with multiple myeloma (MM). Are all myelomas preceded by an MGUS state? What are the evolution patterns of the serum M-proteins and/or FLC prior to the onset of MM? How do the genetic abnormalities progress over time from MGUS to MM in the same patient? Which mechanisms maintain the plasma cell clone in a stable MGUS state and which trigger the progression to MM?5

In this issue of Blood, Landgren and colleagues report that among 77,476 healthy adults enrolled in a prospective Cancer Screening Trial, 71 individuals developed MM.2 In all patients, there were stored serum samples obtained from 2 to 10 years prior to the diagnosis of MM. Serum protein electrophoresis, immunofixation, and kappa-lambda serum FLC assays were performed to determine the prevalence of MGUS and to longitudinally characterize the evolution patterns of the M-proteins prior to the diagnosis of MM. All of the 71 patients who had developed MM had a preceding MGUS, with 75% of them having a detectable M-protein 8 or more years prior to the diagnosis of MM. Interestingly, in about half of the patients, the serum M-protein and the involved FLC showed a year-by-year increase prior to the diagnosis of myeloma. Weiss and colleagues also report on the prevalence of MGUS in 30 patients with MM in whom there was available serum stored by the US Department of Defense Serum Repository.3 These sera were obtained during the mandatory blood tests performed on active US military service members and were collected 2 to 15 years prior to the MM diagnosis. A preceding monoclonal gammapathy was detected in 90% of the patients (27 of the 30). The authors also studied the serial changes in the levels of serum M-proteins and FLC prior to the diagnosis of MM and found that in 7 of 10 patients with sufficient longitudinal available samples, there was a progressive increase in the FLC ratio, with or without a corresponding change in the intact immunoglobulin level prior to the diagnosis of MM.

These articles answer 2 important questions about MGUS. First, virtually all cases of MM are preceded by MGUS. Second, the evolution patterns of M-protein/FLC before the development of MM have been characterized: 30% to 50% had a stable MGUS state until MM developed while 50% to 70% of the patients showed a gradual and progressive increase in the M-protein and/or involved FLC. The latter pattern likely corresponds with the so-called evolving MGUS, first recognized by our group.4 In fact, it can be speculated that all the “evolving” MGUS are slowly growing myelomas from the beginning.5,6 While the recognition that all myelomas are preceded by MGUS is an important step forward, we do not yet know the precise mechanisms that maintain the MGUS state and the mechanisms that trigger progression from MGUS to MM. Further work should be focused on a better understanding of the molecular basis of the disease. It is hoped that this will result in the identification of novel molecular targets involved in the progression from MGUS to MM and in the development of targeted therapies for patients with MGUS, particularly for those at high risk of progression. This could also result in restoring the MGUS state in patients who have already evolved to MM.
Are all myelomas preceded by MGUS?

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