Second, assuming there is clinical benefit, what is the optimal way of following MGUS? Experts recommend annual follow-up with monitoring of monoclonal protein (M-protein). However, we do not know if subsequent development of myeloma is generally detected at the time of scheduled follow-ups or in-between these appointments when patients present with symptoms. If the latter were true, this would argue against routine follow-up. In both studies by Landgren et al and Weiss et al, half of the patients who developed myeloma had relatively stable M-protein and none were high risk according to the Mayo Clinic model. Therefore, monitoring of M-protein may be less important than once thought. Perhaps surveillance for CRAB signs (hypercalcemia, renal failure, anemia, and bone lesions) may be more useful. After all, treatment is not indicated in smoldering myeloma.

Finally, should clinicians use a higher threshold when ordering tests to look for monoclonal gammopathy? MGUS is by definition and clinical intention almost always an incidental finding. One could argue that every MGUS diagnosed is a failed clinical diagnosis of multiple myeloma and related disorders. Routine screening for MGUS is not indicated.

Since its first description by the Swedish hematologist Jan Gosta Waldenström in 1952, the clinical significance of MGUS remains to be determined.

Ronald S. Go
Center for Cancer and Blood Disorders, Gundersen Lutheran Health System, La Crosse, WI
Leah M. Doyle
Gundersen Lutheran Medical Foundation, La Crosse, WI

Response

Multiple myeloma is universally preceded by a prolonged premalignant stage: novel clinical insights and future directions

Go and Doyle address important clinical questions based on our recent study showing that multiple myeloma (MM) is universally preceded by a prolonged premalignant stage. Although the questions raised are not directly related to our paper, which focused primarily on a key biologic question, they are commonly encountered in clinical practice and worth discussing.

Routine screening for MGUS is not indicated. Therefore, almost all individuals diagnosed with MGUS represent incidental cases diagnosed when physicians order a serum protein electrophoresis and/or immunofixation as part of the workup of several common symptoms and laboratory abnormalities. Once diagnosed, patients must be appropriately counseled that MGUS is a premalignant entity with a relatively low risk of progression to MM or related malignancies. In fact, MGUS cases with small (< 1.5 g/dL) IgG monoclonal (M)–proteins and with a normal serum free light chain ratio, represent approximately 40% of all cases, and have only a 2% lifetime probability of developing MM or related malignancies. We have previously recommended that such MGUS cases may not need annual follow-up, but can rather be followed if symptoms suggestive of MM or related disorders occur. In contrast, we feel that MGUS cases with higher risk may benefit from annual follow-up of the M-protein in addition to their usual medical care. Although the value of this is not proven, the test is simple, and, in our opinion, worth doing considering that MM can present with devastating bone complications that may be preventable in some patients if a significant rise in the M-protein is detected in time.

Although, for the individual patient, it is currently not possible to predict whether the underlying MGUS will remain benign or transform to MM, from a population standpoint the significance of MGUS has been well characterized. Several studies have determined the risk of transformation of MGUS patients over time, and identified risk factors for such transformation. In addition to malignant transformation, MGUS patients also have a higher risk of several pathologic conditions, including fractures and deep vein thrombosis. Furthermore, recent data suggest that MGUS cases (compared with the general population) have a significantly reduced life expectancy and an excess risk of dying from bacterial infections and heart, liver, and renal diseases, although this may be related to the various underlying medical conditions that led to the detection of the MGUS. Additional clinical and epidemiologic studies of MGUS are needed.

Our recent observation that MM is universally preceded by a prolonged premalignant stage, with up to 75% of MM patients having detectable M-protein 8 or more years before diagnosis of the malignancy, fills a key gap in the present literature on myelomagenesis. Simultaneously, we found that stable M-protein or free light chain levels do not exclude the development of MM...
To the editor:

Does HUMARA assay for assessment of clonal hematopoiesis have shortcomings?

Determination of clonality based on assays of inactivation of genes encoded on the X chromosome has provided important insights into the origins of neoplastic diseases. The following characteristics make a clonality assay informative: (1) the gene being assayed must undergo X inactivation such that only one allele is expressed in a somatic cell in females; (2) the gene of interest should be sufficiently polymorphic so as to be informative in a reasonably high proportion of the population; (3) the assay should be quantitative because skewing of X inactivation is a normal biologic process determined by the proportion of cells with an active paternal or maternal X chromosome that occurs randomly during embryogenesis; and (4) the assay should be sufficiently robust so that accurate determinations applicable to a variety of tissues can be made at embryogenesis.

To the editor:

Does HUMARA assay for assessment of clonal hematopoiesis have shortcomings?

Determination of clonality based on assays of inactivation of genes encoded on the X chromosome has provided important insights into the origins of neoplastic diseases. The following characteristics make a clonality assay informative: (1) the gene being assayed must undergo X inactivation such that only one allele is expressed in a somatic cell in females; (2) the gene of interest should be sufficiently polymorphic so as to be informative in a reasonably high proportion of the population; (3) the assay should be quantitative because skewing of X inactivation is a normal biologic process determined by the proportion of cells with an active paternal or maternal X chromosome that occurs randomly during embryogenesis; and (4) the assay should be sufficiently robust so that accurate determinations applicable to a variety of tissues can be made at embryogenesis.

Conflict-of-interest disclosure: The authors declare no competing financial interests.
Response: Multiple myeloma is universally preceded by a prolonged premalignant stage: novel clinical insights and future directions

Ola Landgren, Robert A. Kyle and Vincent Rajkumar

Updated information and services can be found at:
http://www.bloodjournal.org/content/114/11/2356.full.html
Articles on similar topics can be found in the following Blood collections

Information about reproducing this article in parts or in its entirety may be found online at:
http://www.bloodjournal.org/site/misc/rights.xhtml#repub_requests

Information about ordering reprints may be found online at:
http://www.bloodjournal.org/site/misc/rights.xhtml#reprints

Information about subscriptions and ASH membership may be found online at:
http://www.bloodjournal.org/site/subscriptions/index.xhtml