

MONOCLONAL GAMMOPATHY OF UNDETERMINED SIGNIFICANCE (MGUS) AND SMOLDERING WALDENSTROM'S MACROGLOBULINEMIA (SWM)

by Robert A. Kyle, MD



Monoclonal gammopathy of undetermined significance (MGUS) is defined as a monoclonal (M) protein in the serum of 3 g/dL (grams per deciliter) or less, fewer than 10% plasma/lymphocytoid cells in the bone marrow, and no evidence of hypercalcemia, renal insufficiency, anemia, or bone lesions (CRAB) related to the plasma cell proliferative disorder. MGUS is found in 3% of the population 50 years of age or older and in 5% of persons older than 70 years. The M protein may be IgG (69%), IgA (11%), IgM (17%), or biconal (two M-proteins) in 3%.

MGUS is more common in men than women (3.7% versus 2.9%). Patients with an IgG or an IgA MGUS progress to multiple myeloma and, less frequently, to light chain (AL) amyloidosis. Patients with an IgM MGUS progress to lymphoma, Waldenstrom's macroglobulinemia, chronic lymphocytic leukemia, and, rarely, AL amyloidosis. The risk of progression is 1% per year for those with an IgG or an IgA MGUS and 1.5% per year for those with an IgM MGUS. The patient should realize that there is a 99% probability of not developing multiple myeloma, Waldenstrom's macroglobulinemia, etc. within the next year. However, the patient remains at this same risk for as long as he or she lives. Overall the risk of progression is 10% at 10 years, 21% at 20 years, and 26% at 25 years.

The median age at recognition of MGUS is 72 years. The rate of progression or death from plasma cell disorders is 6% at 10 years, 10% at 20 years, and 11% at 25 years, while the rate of death due to other diseases such as cardiovascular and cerebrovascular diseases and nonplasma cells cancer is 53% at 10 years, 72% at 20 years, and 76% at 25 years. Of the 70-year-old patients with MGUS only 20% are discovered during routine medical practice. The remaining 80% are found only if one performs electrophoresis upon a total population of 70-year-old persons. MGUS has been present for a median of 11 years in a 70-year-old person when it is discovered during routine clinical practice.

Risk factors for progression of MGUS to multiple myeloma or Waldenstrom's macroglobulinemia include the size of the M-protein when recognized. The risk of progression at 20 years was 14% when the M-protein value was 0.5 g/ dL or less and 49% for those with an M protein of 2.5 g/ dL. Patients with IgM or IgA monoclonal protein have an increased risk of progression as compared to patients with an IgG monoclonal protein. The presence of an abnormal free light chain (FLC) ratio is an additional risk factor. For example, patients with a serum M protein of 1.5 g/dL or more, IgA or IgM monoclonal protein, and an abnormal FLC ratio had a risk of progression at 20 years of 58%, compared to 5% when none of the risk factors were present.

IgM MGUS is defined as having a serum IgM monoclonal protein of less than 3 g/dL, bone marrow lymphoplasmacytic infiltration less than 10%, and no evidence of anemia, constitutional symptoms (fatigue, fever, night sweats, or weight loss), hyperviscosity, lymphadenopathy, or enlargement of the liver or spleen.

IgM MGUS was diagnosed in 213 Mayo Clinic patients who were residents of the 11 counties of Southeastern Minnesota. During long-term follow-up, 29 (14%) of these 213 patients progressed to symptomatic disease: 17 to non-Hodgkin lymphoma, 6 to Waldenstrom's macroglobulinemia, 3 to chronic lymphocytic leukemia, and 3 to AL amyloidosis. The relative risks were 15-, 262-, 6-, and 16-fold, respectively, when compared to a normal population. The overall risk of progression was approximately 1.5% per year. The level of serum M protein and the serum albumin value at diagnosis were the only independent predictors of progression.

Smoldering Waldenstrom's macroglobulinemia (SWM) is characterized by an IgM monoclonal protein of 3 g/dL or more and bone marrow lymphoplasmacytic infiltration of 10% or more with no evidence of anemia, constitutional symptoms, hyperviscosity, lymphadenopathy, or enlargement of the liver or spleen. Thus, MGUS and SWM are separated only by the size of the M protein and the degree of lymphoplasmacytic infiltration of the bone marrow. Both entities are asymptomatic. In a study from Italy, 35(15%) of 217 patients with IgM MGUS and 45 (22%) of 201 patients with indolent (smoldering) Waldenstrom's macroglobulinemia progressed to symptomatic Waldenstrom's macroglobulinemia. The variables related to progression were the size of the initial M-protein value, hemoglobin level, and gender in both groups.

A few questions for the doctor:

Is there a benefit to the patient and his doctor in identifying MGUS from the standpoint of monitoring and treatment?

It is debatable whether the discovery of MGUS of the IgM type is of great value. Since MGUS is asymptomatic, it is discovered by chance. Treatment is not warranted unless the patient develops symptomatic disease.

What are the key differences between MGUS and Smoldering WM patients?

A MGUS patient is distinguished from a smoldering WM patient by the size of the M protein and the degree of bone marrow infiltration. A smoldering WM patient converts to WM upon the development of anemia, constitutional symptoms, hyperviscosity, lymphadenopathy, or hepatosplenomegaly.

Once a patient is treated is the descriptor of Watch and Wait replaced by remission and relapse? Would that patient descriptor of remission and relapse also apply to one who has had only plasmapheresis?

Following treatment, I think that "watch and wait" should be replaced by response (rather than remission) and relapse (evidence of progression of disease). Plasmapheresis is used only in patients with hyperviscosity. This lowers the IgM value and relieves the symptoms of hyperviscosity. I would not consider this to represent a response. I think that virtually every patient who has symptomatic hyperviscosity syndrome would also have other features of WM requiring therapy.

What percentage of MGUS patients transform to WM versus MM?

In our series of 1384 MGUS patients, 115 (8 %) progressed to multiple myeloma, Waldenstrom's macroglobulinemia, or a related plasma cell disorder. Seventy-five of the 115 progressed to multiple myeloma, 19 to lymphoma, 10 to primary amyloidosis, 7 to Waldenstrom's macroglobulinemia, 3 to chronic lymphocytic leukemia, and 1 to plasmacytoma.

Is it more likely that a MGUS patient with an IgM paraprotein will become a WM patient? Will a MGUS patient with IgG paraprotein more likely become a MM patient?

Almost all IgM MGUS patients who progress will develop non-Hodgkin lymphoma (17 of 213), WM (6 of 213), chronic lymphocytic leukemia (3 of 213), or AL amyloidosis (3 of 213). A MGUS patient with IgG paraprotein may develop multiple myeloma or AL amyloidosis.

References

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Career Highlights: Robert A. Kyle

With the Spring issue of 2008, the *Torch* began a new series, Doctor on Call, in which a leading WM specialist discusses a specific aspect of WM in an article written for the IWMF membership. The *Torch* is proud to have introduced this series with an article by Dr. Robert A. Kyle, clinician and researcher, who has been “on call” for Waldenström’s patients throughout a distinguished career that extends from the era of Dr. Jan Waldenström to the present.

Dr. Kyle earned his medical degree from Northwestern University Medical School following his graduation from the North Dakota State School of Forestry and the University of North Dakota, Grand Forks. He did his residency training in internal medicine at Mayo Clinic—a first affiliation with the institution where he would earn his exemplary reputation as both clinical physician and medical researcher. Following his residency at Mayo Clinic, Dr. Kyle completed a fellowship at Tufts University under the mentorship of William Dameshek, M.D., and a postdoctoral research fellowship from the National Cancer Institute. He then joined Mayo Clinic in 1961. At Mayo Dr. Kyle served as the William H. Donner Professor of Medicine and Laboratory Medicine and as Section Head and Chairman of the Division of Hematology. At present he is Professor of Medicine, Laboratory Medicine, and Pathology at Mayo Clinic College of Medicine.

In 1963 Dr. Kyle performed the first bone marrow transplant at Mayo Clinic. In the course of his career he coined the terms “Monoclonal Gammopathy of Undetermined Significance” and “Smoldering Multiple Myeloma”, as well as “Idiopathic Bence Jones Proteinuria.” He is recognized for landmark contributions in the epidemiology of monoclonal gammopathy of undetermined significance. At the Mayo Clinic College of Medicine, moreover, his reputation is that of a tireless educator, having helped train over 200 practicing hematologists. He was also named Teacher of the Year in Internal Medicine. Judging from the warm blend of wit and wisdom he exhibits at the Ask the Doctor sessions of the IWMF Educational Forums, Dr. Kyle must have been a perennial favorite with the students at the College of Medicine.

Dr. Kyle’s research has been published extensively, including more than 750 peer-reviewed articles, and he has made a number of important contributions to the medical literature. He has been co-editor of four editions of *Neoplastic Diseases of the Blood* and co-editor of three editions of *Myeloma Biology and Management*.

Outside of the laboratory and the classroom, Dr. Kyle has served his profession with distinction. For twelve years he was Chairman of the Myeloma Committee of the Eastern Cooperative Oncology Group. He hosted the IVth International Workshop on Multiple Myeloma and the VIIIth International Symposium on Amyloidosis, both in Rochester, MN. He served as Secretary-General of the International Society of Hematology. Currently he is on the Board of Directors and is Chairman of the Scientific Advisory Board of the International Myeloma Foundation. He is also Chairman of the Scientific Advisory Committee of the International Waldenström’s Macroglobulinemia Foundation and President of the International Society of Amyloidosis. National and international acknowledgement of his professional status is seen in the designations of Master, American College of Physicians, and honorary membership in the Royal Society of Pathologists, London.

In his spare time, Dr. Kyle has become well known as a medical historian and philatelist with a specific interest in medicine and stamps.

In the course of his career, Dr. Kyle has received numerous prestigious awards. He has been recognized as the first recipient of the Robert A. Kyle Award for Waldenstrom's Macroglobulinemia Foundation, first recipient of the Robert A. Kyle Lifetime Achievement Award from the International Myeloma Foundation, Mayo Clinic's Henry S. Plummer Distinguished Internist Award, Mayo Clinic's Distinguished Clinician Award, and Mayo Clinic's Distinguished Alumni Award. In 2007 he was also recipient of the David Karnofsky Memorial Award from the American Society of Clinical Oncology.

To members of the IWMMF, Dr. Robert Kyle is familiar as Chairman of the Scientific Advisory Committee and the popular moderator of the Ask the Doctor sessions at the annual Educational Forum. The highlights of Dr. Kyle's career make clear the debt of gratitude owed by the IWMMF to this distinguished hematologist for his continuing service and guidance.