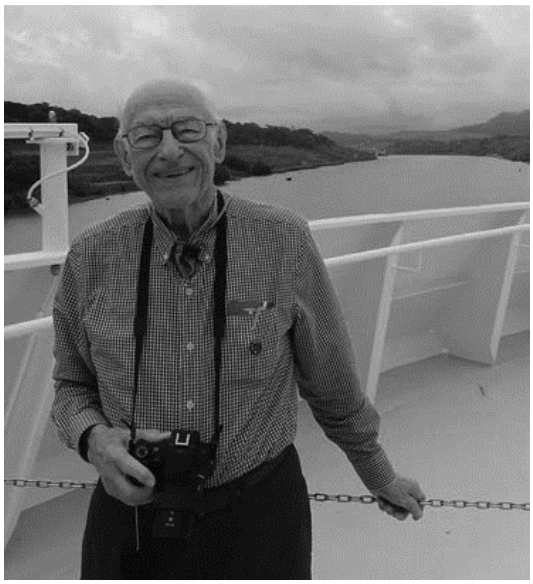
IGM MGUS, SMOLDERING WALDENSTROM'S MACROGLOBULINEMIA, AND WALDENSTROM'S MACROGLOBULINEMIA

BY ROBERT A. KYLE, MD



Dr. Robert A. Kyle

Robert A. Kyle, MD, of Mayo Clinic Rochester, our "Doctor on Call" for this issue of the* IWMF Torch*, needs little in the way of introduction to our membership. Dr. Kyle has been a supporter of the IWMF since its earliest days, serving as Chair of our Scientific Advisory Committee from the time the Committee was established until 2017 and continuing to serve as IWMF Board advisor. Many reading this issue are sure to recall Dr. Kyle's engagement in lively discussions from the podium as he moderated a panel of WM experts at IWMF Educational Forums. Earlier this year, we celebrated Dr. Kyle's 90th birthday in the April 2018 issue of the* IWMF Torch*. Dr. Kyle's status today as a preeminent expert in WM is rooted in his personal friendship with Dr. Jan Waldenström and supported by his long career as a researcher and clinician at Mayo Clinic. In this article, entitled "IgM MGUS, Smoldering Waldenstrom's Macroglobulinemia, and Waldenstrom's Macroglobulinemia," Dr. Kyle reports the most recent research on the status of the so-called "precursor conditions" to WM and their relationship to the development of active disease.

Although the term "monoclonal gammopathy of undetermined significance" (MGUS) was introduced in 1978, efforts in the area had begun a half century before by Theodor Svedberg and his graduate student, Arne Tiselius. They demonstrated that certain proteins in the blood could be separated on the basis of their electric charge, but it was not until 1951 that Tiselius and Henry Kunkel developed a practical laboratory technique for electrophoresis of the serum. Before this approach, electrophoresis required the effort of one technician for an entire day to examine the serum of one patient. This, of course, was impractical for general usage.

In 1944, Jan Waldenström described two patients that we recognize today as having "Waldenstrom's macroglobulin-emia." Even more importantly, he described the concept of monoclonal and polyclonal gammopathies in 1961. This was fundamental because the former can be associated with a malignant or serious condition (multiple myeloma, Walden-strom's macroglobulinemia, AL (light chain) amyloidosis) or a potentially malignant condition (MGUS), compared to a polyclonal gammopathy, which is secondary to an inflamma-tory process such as a rheumatic disorder or liver disease and does not progress to a malignancy.

MGUS occurs in older persons, with 98% being 40 years of age or greater. Its frequency increases with age. About 3% of a normal population 50 years of age or older have MGUS, and approximately 5% of normal people greater than 70 years of age have it. However, we have seen MGUS in two teenagers and several persons in their 20s in a large normal population. MGUS is recognized at an average age of about 72 years, and slightly more than one-half of those affected are male. Almost 4% of men and 3% of women above 50 years of age have a MGUS.

The rate in men is similar to women who are a decade older, suggesting that women "age" more slowly than men. In people older than 85 years of age, the prevalence was almost 9% of men and 7% of women. The incidence of MGUS is twice as high in African Americans. The size of the monoclonal protein does not increase with advancing age. The frequency of MGUS is not greater in those who seek medical care frequently than in those who infrequently see a physician.

The immunoglobulin type is IgG in about 70%, IgA in 12%, IgM in 15%, and biclonal (two monoclonal proteins) in 3% of persons. The size of the M-spike in the serum protein electrophoretic pattern is less than 1.0 g/dL in 60% and greater than 2.0 g/dL in only 5% of persons. The light chain type is kappa in about 60% of individuals and lambda in the remainder. The level of uninvolved immunoglobulins (IgG or IgA) is reduced in about one-third of persons with an IgM monoclonal gammopathy. Approximately one-third of patients with MGUS have an abnormal kappa to lambda free light chain ratio. Examination of the urine reveals a monoclonal light chain (kappa or lambda) in about 30% of persons. The amount of urinary light chain is modest, with the majority of patients having less than 150 mg in a 24 hour urine specimen. Examination of the bone marrow, if done, usually contains less than 5% monoclonal plasma cells or lymphocytes, and must be less than 10% to qualify as a MGUS.

During long-term follow-up of more than 1,000 persons with MGUS, the risk of developing multiple myeloma was increased 24-fold, lymphoma with an IgM monoclonal protein was increased 1.6-fold, AL amyloidosis nearly 9-fold, WM 47.5-fold, and chronic lymphocytic leukemia 0.6-fold when compared to a normal population. These conditions developed in about 10% of patients with MGUS, which is six times higher than one would expect in a normal population. The risk of progression of MGUS was approximately 10% at 10 years, almost 20% at 20 years, 28% at 30 years, and 36% at 35 years if one excludes death from heart disease, stroke, or other malignancies such as cancer of the breast, prostate, lung, colon, or kidney. However, if one includes death from these conditions, only 10% of patients with MGUS overall developed multiple myeloma, lymphoma, AL amyloidosis, or WM. The rest died of conditions unrelated to these disorders. Sex, age at diagnosis, or duration of follow-up did not play a role in progression of MGUS. The M-protein disappeared during follow-up in 5% of this large series, but in the majority of persons, treatment with corticosteroids for a condition unrelated to the plasma cell disorder was responsible. The overall survival of patients with MGUS was shorter than that of a comparable normal population.

We estimate that an MGUS, when discovered "accidentally" in clinical practice, has likely been present for at least a decade.

In this discussion, we will emphasize IgM, which accounts for approximately 15% of all monoclonal gammopathies. IgM MGUS is characterized by the presence of a serum IgM monoclonal protein less than 3 g/dL; a bone marrow, if done, containing fewer than 10% lymphoplasmacytic cells; the absence of symptomatic anemia, enlargement of lymph nodes, liver or spleen; and no hyperviscosity of the blood. In addition, there are no constitutional symptoms such as unexplained fatigue, fever, night sweats, or weight loss. MGUS is completely asymptomatic and is usually found when the physician is examining the patient's blood for an unrelated condition.

The risk of progression among patients with IgM MGUS is almost 11 times that of a normal, comparable population. The risk of progression to non-Hodgkin's lymphoma is increased 10.5-fold, AL amyloidosis 13-fold, and WM 288-fold. The risk of progression among patients with IgM MGUS is about 2% per year for the first 10 years and then approximately 1% per year thereafter.

The initial concentration of the monoclonal protein and the serum free light chain ratio are the most important risk factors for progression.

Patients with IgM MGUS who have an abnormal free light chain ratio and a serum M-protein level greater than or equal to 1.5 g/dL have a risk of progression at 20 years of 55%, compared to 41% of patients with one of these risk factors and only 20% of patients with neither risk factor. The risk of progression was higher when there was a reduced concentration of both uninvolved immunoglobulins (IgG or IgA).

It is likely that virtually all patients who have WM have had an initial IgM MGUS followed by smoldering Waldenstrom's macroglobulinemia (see discussion of smoldering disease below), but these intermediate conditions are often not recognized in clinical practice.

"Smoldering Waldenstrom's macroglobulinemia" (SWM) is characterized by an IgM monoclonal protein greater than or equal to 3 g/dL and/or bone marrow lymphoplasmacytic infiltration greater than or equal to 10%. These patients have no symptomatic anemia or enlargement of the liver or spleen related to the IgM protein. There is no hyperviscosity, and patients have no constitutional symptoms such as unexplained fatigue, weight loss, or night sweats.

In contrast to IgM MGUS, 90% of patients with SWM progress to symptomatic WM requiring therapy and 10% to AL amyloidosis. The likelihood of progression is 6% at one year, almost 40% at three years, and 60% at five years of follow-up. The major risk factor for progression is the number of lymphoplasmacytic cells in the bone marrow, the size of the serum M-protein, and the hemoglobin value at diagnosis. At ten years follow-up, 70% of patients with a serum M-spike greater than or equal to 3 g/dL and bone marrow containing greater than or equal to 10% monoclonal lymphoplasmacytic cells progressed to symptomatic WM, compared to 50% in those with an M-protein less than or equal to 3 g/dL and a bone marrow containing greater than or equal to 10% lymphoplasmacytic cells. The risk of progression of IgM MGUS is about 1.5% per year, compared to 12% per year for patients with smoldering disease.

The diagnosis of "active WM" requires the presence of symptoms such as anemia, enlargement of the liver or spleen, hyperviscosity, or constitutional symptoms; the presence of a monoclonal IgM protein of any size; and a bone marrow containing 10% or more cells with lymphocytoid or plasmacytoid features (lymphoplasmacytic lymphoma). The lymphoplasmacytic infiltration has the same morphologic features as IgM MGUS and SWM.

Patients with smoldering disease should be observed closely without therapy. The history and physical examination as well as determination of the hemoglobin and serum M-protein should be reevaluated at 3-12 months initially, depending on the clinical and laboratory findings.
At this time, the consensus is that patients should not be treated until active WM develops.

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