

IgM Monoclonal Gammopathy of Undetermined Significance (MGUS) and Smoldering Waldenström's Macroglobulinemia (SWM)

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Abstract

Monoclonal gammopathy of undetermined significance of IgM class (IgM MGUS) was diagnosed in 213 Mayo Clinic patients who were residents of 11 counties in Southeastern Minnesota from 1960 to 1994. During long-term follow-up 29 (14%) developed non-Hodgkin lymphoma (n = 17), Waldenström's macroglobulinemia (n = 6), chronic lymphocytic leukemia (n = 3), and AL amyloidosis (n = 3) with relative risks of 15-, 262-, 6-, and 16-fold, respectively. The cumulative probability of progression to one of these disorders was 10% at 5 years, 18% at 10 years, and 24% at 15 years, approximately 1.5% per year.

Forty-eight patients with SWM were identified at Mayo Clinic from 1974 to 1995. During 285 cumulative person-years of follow-up (median, 15.4 years) 34 (71%) progressed to Waldenström's macroglobulinemia (WM), 1 to AL amyloidosis, and 1 to lymphoma (total, 36 [75%]). The cumulative probability of progressing to WM, amyloidosis, or lymphoma was 6% at 1 year, 39% at 3 years, and 59% at 5 years (12% per year).

Report

MGUS is characterized by a serum M-protein concentration < 3.0 g/dL; < 10% clonal plasma cells in the bone marrow and the absence of end-organ damage (CRAB: hypercalcemia, renal insufficiency, anemia, and bone lesions) related to the plasma cell proliferative disorder.^{1,2} Among patients with MGUS, 15%-20% have the IgM subclass. MGUS of the IgM class progresses most often to lymphoma or Waldenström's macroglobulinemia while IgA and IgG MGUS progress to multiple myeloma, primary amyloidosis (AL) or a related plasma cell disorder.

IgM MGUS was recognized in 242 patients at the Mayo Clinic from 1956 to 1978. The median duration of follow-up of patients

with MGUS was 7 years with a total of 1714 patient years. In 40 (17%) of the 242 patients with MGUS, a malignant lymphoid disorder developed during follow-up. These lymphoid disorders consisted of Waldenström's macroglobulinemia in 22, lymphoma in 6, chronic lymphocytic leukemia in 1, AL amyloidosis in 2, and an unclassified lymphoproliferative disorder in 9. The median duration from recognition of the M-protein until the development of Waldenström's macroglobulinemia was 8 years. The median duration of survival after the diagnosis of WM in 22 patients was 6.5 years. In addition, 19 (8%) of the 242 patients with MGUS had an increase of the M-protein of > 0.5 g/dL.³

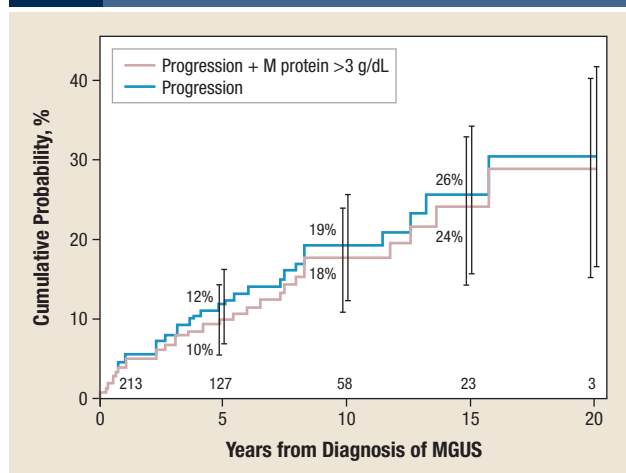
MGUS was recognized in 213 Mayo Clinic patients who were residents of the 11 counties in Southeastern Minnesota from 1960 to 1994. Fifty-eight percent were men and 42% were women. The median age at diagnosis was 74 years (range, 24-94 years). Three patients were younger than 40 years of age while almost two thirds were older than 70 years. The value of the serum M-protein at diagnosis ranged from unmeasurable to 2.6 g/dL (median, 1.2 g/dL). The M-protein was > 1.0 g/dL at diagnosis in 53%. The level of uninvolved immunoglobulins (normal, polyclonal, or background) was reduced in 35% of 129 patients whose immunoglobulin concentration was determined quantitatively. Immunofixation of a concentrated urine specimen revealed a monoclonal kappa light chain in 19%, lambda light chain in 8%, and no monoclonal light chain in 73%. The initial hemoglobin value ranged from 5.9 to 18.9 g/dL (median, 14.0 g/dL). Seventeen percent had a hemoglobin value < 12.0 g/dL and in 4% it was < 10 g/dL. However, the anemia was caused by conditions other than the IgM protein and consisted of myelodysplasia, renal insufficiency, iron deficiency, etc. The serum albumin value ranged from 1.9 g/dL to 4.5 g/dL (median, 3.4 g/dL). Only 14% of patients had an albumin value < 3 g/dL. The serum creatinine level was ≥ 2.0 mg/dL in 7%, but this was not related to the IgM monoclonal protein. Six percent had a positive cryoglobulin. The bone marrow was examined in 27 patients, and all had fewer than 10% lymphoplasma cell cells in the aspirate.

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Figure 1 Probability of Progression in 213 Patients

Patients were residents of southeastern Minnesota in whom monoclonal gammopathy of undetermined significance (MGUS) of IgM class was diagnosed from 1960 through 1994. Curve shows probability of progression of MGUS to lymphoma, Waldenström's macroglobulinemia, primary amyloidosis, or chronic lymphocytic leukemia. Bars show 95% confidence intervals. Numbers at bottom of the horizontal axis are numbers of patients at risk at each interval. This research was originally published in *Blood*. Robert A. Kyle, et al., Long-term follow-up of IgM monoclonal gammopathy of undetermined significance. *Blood*. 2003;15:3759-3764. © the American Society of Hematology.

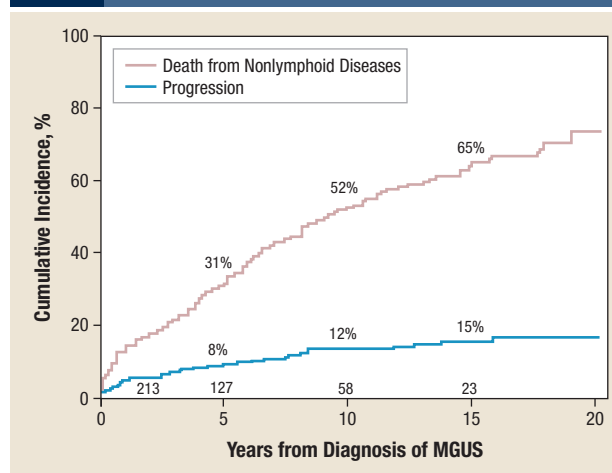
The 213 patients were followed up for 1567 person years (median, 6.3 years per patient). During the long-term follow-up 29 (14%) developed non-Hodgkin lymphoma ($n = 17$; expected, 1.1); Waldenström's macroglobulinemia ($n = 6$; expected, 0.02); chronic lymphocytic leukemia ($n = 3$; expected, 0.53); and AL amyloidosis ($n = 3$; expected, 0.18). The relative risk of progression in the 213 IgM patients was 15.9-fold higher in the patients with IgM MGUS than in the white population of the Iowa Surveillance, Epidemiology and End Results Program. The cumulative probability of progression to one of these disorders was 10% at 5 years, 18% at 10 years, and 24% at 15 years: approximately 1.5% per year (Figure 1).

The risk persisted even after 20 years of follow-up. Death from cardiovascular or cerebrovascular diseases and malignancies unrelated to lymphocytes or plasma cells was 31% at 5 years, 52% at 10 years, and 65% at 15 years. In the competitive model, the rate of progression of IgM MGUS to lymphoplasmacytic malignancies was 8% at 5 years, 12% at 10 years, and 15% at 15 years (Figure 2). The survival of patients with IgM MGUS was 7.0 years compared to 10.8 years for Minnesota residents of matched age and sex.

The risk of progression to a lymphoplasmacytic neoplasm was 15.9 times that expected on the basis of incidence rates for those conditions in the general population. The risk for progression was increased 14.8-fold for non-Hodgkin lymphoma, 262-fold for WM, 16.3-fold for AL amyloidosis, and 5.7-fold for chronic lymphocytic leukemia.

The hemoglobin level, serum albumin value and the sedimentation rate were significant while the serum M-protein concentration was of borderline significance in the univariate model. Independent predictors of progression with multivariate analysis included the size of the serum M-protein level at diagnosis and the serum albumin value.

The risk for progression was directly related to the level of the serum M-protein at the time of diagnosis of MGUS. The risk of pro-

Figure 2 Competitive Model in 213 Patients

Patients were residents of southeastern Minnesota in whom monoclonal gammopathy of undetermined significance (MGUS) of IgM class was diagnosed from 1960 through 1994. Upper curve shows probability of dying of nonlymphoid diseases. Lower curve shows probability of progression to lymphoma or a related disorder. This research was originally published in *Blood*. Robert A. Kyle, et al., Long-term follow-up of IgM monoclonal gammopathy of undetermined significance. *Blood*. 2003;15:3759-3764. © the American Society of Hematology.

gression to lymphoma or related malignancy 10 years after recognition of MGUS was 14% with an initial M-protein value of 0.5 g/dL or less, 26% for 1.5 g/dL, 34% for 2.0 g/dL, and 41% for those with a serum spike of 2.5 g/dL. The risk for progression to lymphoma or a related disorder at 10 years with an initial M-protein value of 1.5 g/dL was 1.8 times the risk for progression with an initial value of 0.5 g/dL or less; for an initial value of 2.0 g/dL, it was 2.8-fold increased and for an initial value of 2.5 g/dL it was increased 3.1-fold.⁴ The risk persisted even after 20 years of follow-up.

Management of patients with IgM MGUS is not clearly defined. The physician must not alarm the patient and cause psychological stress. At the same time, the patient must be told to seek medical evaluation if they develop unexplained symptoms such as fever, night sweats, fatigue, or weight loss. Patients should be evaluated 6 months after recognition of MGUS to exclude the possibility of an evolving WM. If the patient is stable at 6 months and if the serum M-protein is ≥ 1.5 g/dL, the patient should be followed at annual intervals. If the M-protein is < 1.5 g/dL the patient may be followed at 3-5 year intervals. A brief history and physical should be done and the minimal laboratory tests should consist of a hemoglobin determination and performance of serum protein electrophoresis at follow-up. If there are abnormalities in these tests or if the patient has unexplained symptoms, further evaluation is necessary.

Smoldering Waldenström's macroglobulinemia is defined as having a serum monoclonal protein ≥ 3 g/dL and/or $\geq 10\%$ bone marrow lymphoplasmacytic infiltration but no evidence of constitutional symptoms, symptomatic anemia, lymphadenopathy, hepatosplenomegaly, or hyperviscosity. The hemoglobin was < 10 g/dL in 8% but this was due to causes other than the lymphocytic plasma cell proliferative disorder. The serum M-protein was < 3 g/dL in 25% and 4 g/dL or more in 21%. The bone marrow lymphoplasmacytic infiltration was $< 10\%$ in 6% of patients but was $> 50\%$ in 27% of the SWM patients at the time of diagnosis. Forty-

eight patients with SWM were identified at Mayo Clinic from 1974 to 1995. During 285 cumulative person-years of follow-up (median, 15.4 years) 34 (71%) progressed to Waldenström's macroglobulinemia, 1 to AL amyloidosis and 1 to lymphoma (total, 36 [75%]). On the basis of the Iowa Surveillance, Epidemiology and End Results Program one would expect 0.004 cases of WM; the relative risk of progression was increased 8034-fold. The cumulative probability of progressing to WM, amyloidosis, or lymphoma was 6% at 1 year, 39% at 3 years, and 59% at 5 years (12% per year). The median time of progression from recognition of smoldering Waldenström's macroglobulinemia to symptomatic WM was 4.6 years. Seventy-five percent of the patients with SWM have died, indicating a mature follow-up. Risk factors for progression with univariate analysis included hemoglobin, size of serum M-protein, type of serum light chain, free light chain ratio, reduction of uninvolved immunoglobulins, presence of monoclonal urinary light chain, serum albumin value, and number of lymphoplasmacytic cells in the bone marrow. On multivariate analysis, the size of the serum M-protein, hemoglobin value, and number of lymphoplasmacytic cells in the bone marrow at diagnosis were independent risk factors for progression.

The patient must be told to seek immediate medical care if fever, night sweats, unexplained weight loss, or increasing fatigue occur. Patients should be reevaluated 6 months after recognition of SWM. A physical examination is helpful in detecting enlargement of the liver, spleen, or lymph nodes. Minimal laboratory studies include measurement of hemoglobin and serum protein electrophoresis. These tests should be repeated at annual intervals. The free light chain ratio is of no practical value in monitoring the patient. If any patient develops constitutional symptoms, they should seek immediate medical care. At present, there is no role for chemotherapy for SWM.

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