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IgM Monoclonal Gammopathy of Undetermined Significance and Smoldering Waldenström's Macroglobulinemia

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Abstract

Immunoglobulin M monoclonal gammopathy of undetermined significance (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 (WM; 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. Smoldering WM was identified in 48 patients at Mayo Clinic from 1974 to 1995. During follow-up, 33 of the 48 patients progressed to symptomatic WM. The median time to progression was 4.6 years. The risk of progression to WM was 6% at 1 year, 39% at 3 years, and 55% at 5 years.

Keywords

Immunoglobulin; Light chain; Serum M protein; Waldenström

Report

Immunoglobulin (Ig) M monoclonal gammopathy of undetermined significance (IgM-MGUS) is defined as a serum IgM monoclonal protein < 3 g/dL, bone marrow lymphoplasmacytic infiltration < 10%, and no evidence of constitutional symptoms, anemia, hyperviscosity, lymphadenopathy, or hepatosplenomegaly related to the lymphoplasmacytic process.^{1–3}

IgM monoclonal gammopathy of undetermined significance was found in 56% of 430 patients with an IgM monoclonal protein seen at Mayo Clinic between 1956 and 1978.⁴ Gobbi et al found an IgM-MGUS in approximately 20% of patients with MGUS and in 30% of patients who had an IgM monoclonal protein.⁵

Monoclonal gammopathy of undetermined significance was diagnosed in 213 Mayo Clinic patients from 1960 to 1994 who were residents of 11 counties in southeastern Minnesota.^{2,6} Fifty-eight percent of the 213 patients were men, and 42% were women. The median age at diagnosis was 74 years (range, 24–94 years). The size of the serum M protein at diagnosis ranged from unmeasurable to 2.6 g/dL (median, 1.2 g/dL). Only 53% of patients had an M

protein value > 1.0 g/dL at diagnosis. The light chain was kappa in 70% and lambda in 30%. The concentration of uninvolved immunoglobulins was reduced in 35% of the 129 patients whose initial Ig concentration was determined quantitatively. A monoclonal light chain was found in the urine in 27%. The hemoglobin level was < 12.0 g/dL in 17%, but the anemia was caused by conditions other than the monoclonal gammopathy in all. The serum albumin level ranged from 1.9 g/dL to 4.5 g/dL (median, 3.4 g/dL). Fourteen percent had an albumin level < 3 g/dL. The liver was palpable in 10% and spleen in 2%. The 213 patients were followed for 1567 person-years (median, 6.3 years), during which time 71% died. During the long-term follow-up, 29 (14%) of these 213 patients developed non-Hodgkin lymphoma (n = 17), Waldenström's macroglobulinemia (WM; n = 6), chronic lymphocytic leukemia (CLL; n = 3), and AL amyloidosis (n = 3), with relative risks of 15-, 262-, 6-, and 16-fold, respectively (Table 1). Progression occurred slowly in most patients, but some progressed more rapidly. 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. Patients were at risk of progression even after having stable MGUS for 20 years. Risk of death as a result of other diseases such as cardiovascular and cerebrovascular diseases and cancers not of lymphoplasmacytic origin were 31% at 5 years, 52% at 10 years, and 65% at 15 years. Patients with IgM-MGUS had a shorter median survival time than expected for Minnesota residents of matched age and sex, 7 years versus 10.8 years ($P < .001$). The number of patients with progression to a lymphoid neoplasm or a related disorder (29 patients) was 15.9 times that expected on the basis of incidence rates for those conditions in the general population.

Smoldering WM (SWM) is defined as a serum IgM (monoclonal) protein > 3 g/dL and/or > 10% bone marrow lymphoplasmacytic infiltration but no evidence of symptomatic anemia, constitutional symptoms, or hyperviscosity. A total of 48 patients with SWM were identified at Mayo Clinic from 1974 to 1995. Patients with a diagnosis of CLL or lymphoma or a history of any antineoplastic therapy were excluded. The median age at diagnosis was 63 years (range, 39–87 years). Only 1 patient (2%) was aged < 40 years, but 14% were aged < 50 years. Of the patients, 32 (67%) were men, and 16 (33%) were women. At diagnosis, hepatomegaly was noted in 10%, splenomegaly in 4%, and lymphadenopathy in 8%. The initial hemoglobin level ranged from 8.7 to 15.3 g/dL (median, 11.8 g/dL). The anemia in all 4 patients with an initial hemoglobin < 10 g/dL was due to other causes such as myelodysplastic syndrome, bronchopleural fistula, Barrett's esophagus, and bleeding from warfarin administration. The initial median leukocyte level was $5.7 \times 10^9/L$, and the median platelet value was 285.5×10^9 . The serum monoclonal protein level at the time of diagnosis ranged from 1.5 g/dL to 5.2 g/dL (median, 3.3 g/dL). Twelve (25%) were < 3 g/dL, and 10 (21%) were 4 g/dL. IgM kappa was present in 76% and IgM lambda in 20%, and 4% were biclonal. Immunofixation of the urine was positive in 97% (kappa 80%, lambda 17%, indeterminate 3%) of those tested. The amount of the urine M protein ranged from unmeasurable to 1.4 g/24 h (median, 0.04 g/24 h). Serum albumin ranged from 2.5 g/dL to 4.3 g/dL (median, 3.6 g/dL). Five patients (10%) had an albumin level < 3 g/dL. Ten (26%) had a reduction of one uninvolved immunoglobulin, and 8 (21%) had a reduction of both IgG and IgA immunoglobulins. The γ_2 -microglobulin value was available in 21 patients and ranged from 1.5 $\mu\text{g/mL}$ to 4.0 $\mu\text{g/mL}$ (median, 2.1 $\mu\text{g/mL}$). Eighty-one percent were > 1.8 $\mu\text{g/mL}$. Lymphoplasmacytic infiltration of the bone marrow ranged from 3% to 80% (median 30%). Only 3 (6%) had < 10% infiltration, whereas 13 (27%) had 50% infiltration.

The 48 patients were followed for a total of 292 person-years (range, 0.5–22.2 years; median, 3.7 years), during which time 33 (.004 expected from Surveillance, Epidemiology and End Results data; relative risk, 7586) progressed to symptomatic WM. The median time to progression was 4.6 years and usually occurred slowly. The median survival after

progression to symptomatic WM was 5.1 years. The risk of progression to WM was 6% at 1 year, 39% at 3 years, and 55% at 5 years (Figure 1). Seventy-three percent of the patients died, indicating a robust follow-up.

We evaluated sex, hemoglobin level, amount of serum M protein, reduction of uninvolved immunoglobulins, presence of urinary monoclonal light chains, serum albumin level, and the proportion of lymphoplasmacytic infiltration of the bone marrow as risk factors for progression. Significant risk factors for progression with univariate analysis included amount of the serum M protein, hemoglobin level, reduction of uninvolved immunoglobulins, and degree of bone marrow lymphoplasmacytic cell infiltration. Multivariate modeling revealed that the amount of the M protein and the degree of bone marrow infiltration were the most important risk factors.

We conclude that SWM is a distinct clinical entity that needs to be differentiated from IgM-MGUS and symptomatic WM. Neither of these conditions should be treated.

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Figure 1.
Smoldering Waldenström's Macroglobulinemia

Table 1

Progression of Smoldering Waldenström's Macroglobulinemia to Symptomatic Waldenström's Macroglobulinemia

IgM MGUS Southeast Minnesota 1960–1994			
Observed and Expected Progression Rates (N = 213)			
Progression	Observed	Expected*	RR
Lymphoma (NHL)	17	1.1	14.8
Amyloidosis	3	0.18	16.3
Macroglobulinemia	6	0.02	262
CLL	3	0.53	5.7
Total	29	1.83	15.9

* Iowa Surveillance, Epidemiology and End Results Registry.

Abbreviations: CLL = chronic lymphocytic leukemia; Ig = immunoglobulin; MGUS = monoclonal gammopathy of undetermined significance; NHL = non-Hodgkin lymphoma; RR = relative risk