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50 Year Incidence of Waldenström Macroglobulinemia in Olmsted County, Minnesota From 1961–2010: A Population-Based Study With Complete Case Capture and Hematopathologic Review

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Abstract

Objective—To determine the incidence of Waldenström macroglobulinemia (WM) in a strictly defined geographic area over a 50-year period.

Patients and Methods—All residents of Olmsted County with a diagnosis of WM consisting of a monoclonal IgM protein of any size and/or 10% lymphoplasmacytic infiltration of the bone marrow along with anemia, constitutional symptoms, hyperviscosity, lymphadenopathy or hepatosplenomegaly requiring therapy were identified from January 1, 1961 to December 31, 2010. Patients with smoldering Waldenström macroglobulinemia (SWM), lymphoplasmacytic lymphoma (LPL) with an IgG or IgA monoclonal protein, as well as those with an IgM monoclonal gammopathy of undetermined significance (MGUS) were excluded.¹ The peripheral blood smears, bone marrow aspirates and biopsies were reviewed by an experienced hematopathologist.

Results—Twenty-two patients were identified as having WM. The age-adjusted incidence rate for males was 0.92/100,000 (95% CI, 0.44–1.39) and females 0.30/100,000 (95% CI, 0.08–0.53) with an age- and sex-adjusted incidence of 0.57/100,000 (95% confidence interval 0.33–0.81/100,000). When evaluated using a smoothing spline, there was no convincing evidence for a change in the incidence of WM over the last 50 years. Patients diagnosed with WM after 2000 had

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an approximately 2-fold excess mortality compared to the expected population (SMR=2.4, 95% CI 0.64–6.0).

Conclusion—WM is a rare malignancy and the incidence in Olmsted County, Minnesota, has shown virtually no change over the past 50 years.

INTRODUCTION

Waldenström macroglobulinemia (WM) is an uncommon disease characterized by a lymphoplasmacytic lymphoma (LPL) that produces an IgM monoclonal protein.^{1, 2} The size of the monoclonal IgM protein is often > 3 g/dL but a specific level is not required for diagnosis. WM is now recognized as a distinct clinical entity defined by the presence of a monoclonal IgM protein regardless of its size, 10% bone marrow infiltration by small lymphocytes that exhibit plasmacytoid or plasma cell differentiation and a typical immunophenotype (surface IgM⁺, CD19⁺, CD20⁺, CD5^{+/-}, CD10⁻ and CD23⁻) as well as exclusion of other lymphoproliferative disorders, including chronic lymphocytic leukemia and lymphoma.²⁻⁴ The clinical features include constitutional symptoms consisting of weakness and/or fatigue from anemia, fever, night sweats or weight loss. Smoldering Waldenström Macroglobulinemia (SWM) is defined as the presence of a serum monoclonal IgM protein 3 g/dL and/or 10% bone marrow lymphoplasmacytic infiltration but without evidence of end-organ damage such as anemia, constitutional symptoms, hyperviscosity, symptomatic lymphadenopathy or hepatosplenomegaly.⁵ Initiation of therapy is necessary for patients with constitutional symptoms, progressive symptomatic lymphadenopathy or splenomegaly, hemoglobin 10 g/dL, platelets < 100 × 10⁹/L or the presence of symptomatic hyperviscosity, severe sensorimotor peripheral neuropathy, systemic amyloidosis, renal insufficiency or symptomatic cryoglobulinemia from the lymphoplasmacytic proliferative process.⁴

In 2016, 1,270 cases of WM and 1,060 cases of LPL were estimated to be diagnosed in the United States based on data from population-based cancer registries from 45 states and the District of Columbia.⁶ The age-adjusted incidence (2000 US standard population) from 2011–2012 was 0.3/100,000 for WM, 0.3/100,000 for LPL, and 0.6/100,000 for WM/LPL combined. The WM/LPL incidence was higher in males (0.8/100,000) than females (0.4/100,000), and was highest in non-Hispanic whites, intermediate in non-Hispanic blacks, and lowest in Asian Pacific Islanders. In a SEER analysis for 1988–2007, the age-adjusted incidence of WM was 0.38/10⁵ and was higher in men (0.54/100,000) than women (0.27/100,000).⁷ Over that timeframe, there was no statistically significant change in the incidence overall or by sex. WM was not reportable to SEER registries prior to 1988. Phekoo et al., reported an age-adjusted (European standard population) incidence of 0.55/10⁵ for WM in South East England between 1999 and 2001.⁸ Iwanaga et al., reported an age-adjusted incidence (2000 US standard population) for WM/LPL of 0.065/10⁵ in Japan and 0.042/10⁵ in Taiwan from 1996 to 2003; rates in Japan were increasing over this time period but were stable for Taiwan.⁹

The major source of epidemiologic data on WM incidence has been from population-based, central cancer registries^{7, 9, 10} Central registries rely on case-reporting from community

practice, and may include patients with lymphoma who have an incidental monoclonal IgM protein (MGUS) as well as patients with SWM potentially increasing the rate. On the other hand, patients with LPL who did not have serum protein electrophoresis might be overlooked, thus reducing the incidence. True cases may also be misdiagnosed as another indolent lymphoproliferative disorder. Many cases are diagnosed outside of hospitals or large referral centers, and may not get reported to central registries. Finally, cases in central registries are not independently verified by expert hematopathologic review. Indeed, no WM incidence studies have been published with review of the pathology of bone marrow aspirates and biopsies.

It is also difficult to estimate WM incidence rates over a long time period because of changing criteria for diagnosis, changes in clinical practice, differing autopsy rates, variation in methods of diagnostic indexing of medical records, inclusion or exclusion of LPL, and use of different population standards.

These limitations are minimized in Olmsted County, Minnesota because medical care for the population of Rochester, MN and the surrounding Olmsted County has been provided almost exclusively by the Mayo Clinic and the Olmsted Medical Group which includes the medical records for all Olmsted County subjects. The medical, surgical and pathologic diagnoses of significant illness among Olmsted County residents at both institutions have been compiled in a centralized records-linkage system. The relative stability of the local population, particularly in the elderly age groups which are at a higher risk for WM, the unusual centralization of high quality medical care and the centralized diagnostic indexing and records-linkage system for many decades provides an exceptional source for studies of incidence rates and long-term trends in the population of Olmsted County.¹¹ This report describes the incidence rates of WM and the trends over a 50-year period.

METHODS

The records of all Olmsted County residents with a monoclonal IgM protein and bone marrow involvement by a lymphoproliferative disorder were sought in our Mayo Clinic Dysproteinemia Database as well as the Rochester Epidemiology Project which includes the medical records of the Olmsted Medical Group from January 1, 1961 to December 31, 2010. WM was defined as the presence of a monoclonal IgM protein of any size, 10% lymphoplasmacytic infiltration of the bone marrow, and the presence of anemia, constitutional symptoms, hyperviscosity, lymphadenopathy or hepatosplenomegaly requiring therapy.^{3, 12} In cases where there was doubt about the extent of bone marrow involvement due to inadequacy of sample, or lack of availability of an outside specimen for review, we relied on the documentation of definite end-organ damage attributable to the clonal process in making the diagnostic determination of WM. Patients with SWM defined clinically as having a serum monoclonal IgM protein 3 g/dL and/or 10% bone marrow lymphoplasmacytic infiltration without evidence of end-organ damage (anemia, constitutional symptoms, hyperviscosity, lymphadenopathy or hepatosplenomegaly) were excluded.⁵ Patients with LPL but no immunoelectrophoresis or immunofixation were also excluded.

After the study was approved by the Mayo Clinic and Olmsted Medical Group Institutional Review Boards, we searched our computerized database and reviewed the medical records of all patients who had been seen at the two institutions within 30 days after detection of an IgM monoclonal protein and a lymphoplasmacytic infiltration of the bone marrow along with anemia, constitutional symptoms, hyperviscosity, lymphadenopathy or hepatosplenomegaly requiring therapy. Patients presenting with other lymphomas, chronic lymphocytic leukemia, IgM monoclonal gammopathy of undetermined significance (MGUS), smoldering WM or lymphoplasmacytic lymphoma with monoclonal IgG or IgA proteins were excluded. Only those persons who had lived in Olmsted County for at least one year before the diagnosis of a lymphoproliferative disorder were considered to be residents. Persons known to have moved to Olmsted County to facilitate the diagnosis and treatment of symptoms of lymphoproliferative disorders were also excluded.

Follow-up included a review of the medical records of all patients and of the death certificates available for those who had died. Death certificates were requested from the 10 states that allow the purchase of death certificates. All patients were sent a letter of inquiry or contacted by telephone if they had not visited Mayo Clinic in the preceding year.

The peripheral blood smears, bone marrow aspirates, and bone marrow biopsies, when available, were reviewed by a hematopathologist (E.D.M.). Specific features were assessed, including presence or absence of increased background mast cells, presence or absence of a spectrum of lymphocytic to plasmacytoid to true plasma cell morphology¹³ and pattern of bone marrow involvement. Two-color flow cytometric immunophenotyping to assess the B-cell population had been previously performed in 11 cases using the following monoclonal antibodies: CD3, CD5, CD10, CD11c, CD16, CD19, CD20, CD22, CD23, CD45, CD14, and kappa and lambda immunoglobulin light chains. The antibodies to κ and λ light chains were obtained from Caltag/Invitrogen (Carlsbad, CA); all other antibody conjugates were from BD Biosciences. In addition, 6-color plasma cell flow cytometry had been previously performed in two cases using the following antibodies: CD19 PE-Cy7 (Clone SJ25C1; BD Biosciences, San Jose, CA, USA), CD38 APC (Clone HB7; BD Biosciences), CD45 APC-H7 (Clone 2D1; BD Biosciences), CD138 Percp-Cy5.5 (clone MI15; BD Biosciences), and kappa and lambda immunoglobulin light chains (both from Dako, Carpinteria, CA, USA).¹⁴ Immunoperoxidase stains were performed on paraffin sections of the bone marrow biopsy specimens in 10 cases using antibodies directed against CD3 (Leica (Novacastra), CD20 (Dako), CD138 (Dako) and kappa and lambda immunoglobulin light chains (Dako).

Statistical Analysis

The age-, sex-, and calendar year-specific incidence rates of WM were based on data from Olmsted County, Minnesota, using the number of cases of WM in each age/sex/calendar-year group as the numerator, and the corresponding U.S. decennial census population counts for Olmsted County, MN as the denominators.¹⁵ Age- and sex-adjusted incidence rates were calculated by direct standardization to the 2010 United States population. Ninety-five percent (95%) confidence intervals for the incidence rates were calculated based on the Poisson distribution. Temporal trends in the incidence rates were examined using Poisson regression.

RESULTS

Twenty-two patients were identified as having WM from January 1, 1961 to December 31, 2010. The median age at diagnosis was 71.5 years (range 50–94). Males accounted for 68%, while Caucasians constituted 95% of patients. The liver was palpable in 1 patient and the spleen in another. One other patient had palpable lymphadenopathy at diagnosis. The median hemoglobin value was 9.8 g/dL (range 4.0–12.5). The value was ≥ 12 g/dL in 95%, while 57% had a hemoglobin value of ≥ 10 g/dL at diagnosis. The leukocytes ranged from 3.1 to $45.1 \times 10^9/L$ (median 6.9×10^9). The leukocytosis of $45.1 \times 10^9/L$ in a single patient was due to WM and resolved quickly with chemotherapy and did not recur. The platelets ranged from 49×10^9 to 558×10^9 with a median of 296×10^9 . Thrombocytopenia ($< 150 \times 10^9$) was due to a packed bone marrow in two cases and without a recognized cause in one, while the three patients with platelets $> 500 \times 10^9$ were not related to a specific cause. The serum calcium ranged from 8.4–12.1 mg/dL. There was no specific cause of hypercalcemia in the single patient even at autopsy. The median serum creatinine value was 1.1 mg/dL (range 0.7–2.8 mg/dL). In the single patient with an elevated creatinine > 2 mg/dL, the renal insufficiency was attributed to diabetes mellitus and hypertension.

The serum M component ranged from 0.5 to 4.5 g/dL at diagnosis. During the course of their disease only two patients had an M component < 2.5 g/dL (0.5, 2.2 g/dL). IgM κ was present in 76% and the remaining 24% had an IgM λ monoclonal protein. One patient with a large IgM κ had a small IgG λ protein (biclonal) as well. Of the 16 patients who had a 24-hour urine collection within 30 days of diagnosis, 14 had a monoclonal light chain consisting of kappa in 9, lambda in 5 and no monoclonal light chain in 2 patients. Only 2 patients had an M-protein > 1 g/dL (1.2 and 3.8 per 24 hours). The remaining 6 patients had a 24-hour urine collection during the course of their disease and only one had had a monoclonal light chain (kappa, unmeasurable). One uninvolved serum immunoglobulin (IgA or IgG) was reduced in 9 of 15 (47%) patients at diagnosis, while both uninvolved immunoglobulins were reduced in 11 of 15 (73%) during the course of their disease.

The bone marrow aspirate/biopsy was examined in 19 of the 22 (86%) patients and the diagnosis of a lymphoplasmacytic lymphoma was confirmed. The bone marrow aspirate/biopsies were not available for review in three patients but the reports of the bone marrows at the time of diagnosis were consistent with lymphoplasmacytic lymphoma (WM). The peripheral blood specimens contained circulating lymphocytes with a plasmacytoid appearance. Rouleaux formation was often observed. The bone marrow aspirate specimens showed a lymphoplasmacytic infiltrate characterized by a spectrum of small lymphocytes to plasmacytoid lymphocytes to true plasma cells, and were often accompanied by increased mast cells. In the bone marrow biopsies, this infiltrate was present in a nodular, interstitial, and/or paratrabeular distribution. Flow cytometry, when available ($n=11$), confirmed the presence of a CD10-negative, monotypic B-cell population in all cases. A light chain identical, monotypic plasma cell population was also identified by flow cytometry in two cases. One case coexpressed CD5. Paraffin section immunohistochemistry performed on the bone marrow biopsies, when available ($n=11$), confirmed the presence of both monotypic CD20-positive B-cells and monotypic CD138-positive plasma cells.

The age-adjusted incidence rate for males was 0.92/100,000 (95% CI, 0.44–1.39) and females 0.30/100,000 (95% CI, 0.08–0.53). The age- and sex-adjusted annual incidence rate for WM was 0.57/100,000 (95% CI 0.33–0.81 CI) (Table 1). The incidence of WM increased with age (Figure 1). The incidence rate was virtually unchanged throughout the half century of this study (Figure 2, Table 2).

The cause of death was based on information from the patient's clinical record and the death certificates. Infection was the major cause of death in 8 including 1 patient with pulmonary aspergillosis, myelodysplasia 3, WM/lymphoma 3, stroke 2, congestive heart failure from Adriamycin toxicity in one and upper gastrointestinal hemorrhage in one. Most patients who died had advanced, symptomatic WM in addition to the immediate causes of death. Four patients are still alive. The date of diagnosis and the survival of all 22 subjects are provided in Table 3. Over the entire period, WM patients had a 5-fold excess mortality (SMR=5.4, 95% CI 3.2–8.5), although this was much weaker for patients diagnosed after 2000 (SMR=2.4, 95% CI 0.64–6.0).

DISCUSSION

In 1944, Jan Waldenström reported two patients with oronasal bleeding, normochromic anemia, elevated erythrocyte sedimentation rate and lymphadenopathy.¹⁶ This entity, later defined as Waldenström macroglobulinemia, is a well-recognized lympho-plasmacytic malignancy that occurs as a major progression event in the course of IgM MGUS. Data on the incidence of WM are limited. In this study, we found an incidence rate of 0.57 per 100,000 per year based on a long-term study in a stable, geographically well-identified population. Similar to our previous studies on the incidence of multiple myeloma¹⁷, the region studied is well-suited for this purpose due to excellent case ascertainment and high quality medical care. Our results are consistent with other United States epidemiologic studies that have been reported utilizing Surveillance, Epidemiology and End Results (SEER). Groves et al., reported a rate of 0.34/100,000 in males and 0.17/100,000 in females.¹⁰ Similar results of 0.38/100,000 persons per year were reported by Wang et al., utilizing SEER data. The rates in men were higher (0.54/100,000/year) than in women (0.27/100,000/year). The age-adjusted incidence (2000 US standard population) from 2011–2012 was 0.3/100,000/year for WM, 0.3/100,000/year for LPL, and 0.6/100,000/year for WM and LPL combined.⁶ In the United Kingdom, Phekoo et al., found a rate of 0.55/100,000/year in the South Thames Haematology Registry in Southeastern England.⁸

In our study, to ensure complete case ascertainment, we reviewed the records of all Olmsted County residents who had been diagnosed with WM, or lymphoplasmacytic lymphoma with an IgM monoclonal protein. Very few, if any, patients with LPL would not have had an SPEP and immunoelectrophoresis or immunofixation at the Mayo Clinic. We were careful to exclude patients with other lymphoproliferative disorders as well as smoldering WM and those patients with a lymphoplasmacytic proliferation with an IgG or an IgA monoclonal protein. Strict requirements for residency in Olmsted County were utilized. Trained residency clerks supplied with maps, county plat books, city directories and telephone books determined residency status with great precision. Virtually all residents of Olmsted County seek their medical care at Mayo Clinic or the Olmsted Medical Group ensuring complete

ascertainment of new cases. However, the small number of patients with WM is a limitation of this study.

The age and gender distribution of our WM patients were consistent with the typical findings of others. The clinical features consisting of constitutional symptoms and the presence of anemia requiring therapy were also consistent with the typical clinical and laboratory findings in WM. The pathologic features identified in these cases, including circulating lymphoma cells with a plasmacytoid appearance, peripheral blood rouleaux, bone marrow involvement by a spectrum of small lymphocytes to plasmacytoid lymphocytes to true plasma cells in a nodular, interstitial, and/or paratrabecular distribution, and presence of monotypic B-cells and plasma cells are typical for WM/lymphoplasmacytic lymphoma. CD5 coexpression by the B-cells, as was seen in 1 case, has also been previously described.

We show that the incidence of Waldenström macroglobulinemia has remained virtually stable over a long period of time. More importantly, we find that Waldenström macroglobulinemia is a very rare disorder with an incidence of approximately 0.6 per 100,000 per year. Recent attempts to revise the disease definition can artificially increase this incidence dramatically. For example, some have recommended that we eliminate the minimal requirement of 10% or greater clonal marrow involvement, and allow patients with *any* level of bone marrow infiltration to be considered as having Waldenström macroglobulinemia.² However, this will convert most if not all patients with IgM MGUS into Waldenström macroglobulinemia, making it one of the more common malignancies in the world. This scenario highlights how population-based incidence estimates are susceptible to increases of a hundred-fold or larger not due to a real increase but due to tweaks in diagnostic criteria. In this case, our concern is amplified since patients can be harmed by unnecessary diagnostic interventions, inappropriate institution of therapy, and by the ramifications of carrying a diagnosis of malignancy on one's quality of life. Patients with less than 10% clonal infiltration should continue to be considered as having IgM MGUS as defined by the International Myeloma Working Group,¹⁸ since their risk of progression is low, and overall survival has been shown to be similar to the general population.^{19, 20} This rate is several-fold lower than the incidence of multiple myeloma, a closely related plasma cell malignancy.

In summary, this study is the first epidemiologic study to evaluate the clinical, laboratory and pathologic features of WM in a specifically prescribed area and time of diagnosis. Waldenström macroglobulinemia is a rare malignancy with an incidence that is several fold lower than that of multiple myeloma. The incidence of this disease has shown virtually no change during the past half century.

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Abbreviations

MGUS	Monoclonal gammopathy of undetermined significance
SWM	Smoldering Waldenström macroglobulinemia
WM	Waldenström macroglobulinemia

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Figure 1.
Age and Sex-Adjusted Incidence Rates of Waldenström Macroglobulinemia per 100,000
Person-Years in Olmsted County, Minnesota, 1961 through 2010.

Figure 2.
Age and Sex-Adjusted Incidence Rates of Waldenström Macroglobulinemia per 100,000
Person-Years in Olmsted County, Minnesota by Decade, 1961 through 2010.

Table 1

Age- and Sex-Specific Incidence Rates of Waldenström Macroglobulinemia per 100,000 Person-Years in Olmsted County, Minnesota, 1961 Through 2010

	Male		Female		Total	
	No.	Rate	No.	Rate	No.	Rate
Age (yr)						
50–59	7	2.9	2	0.8	9	1.8
60–69	0	0	0	0	0	0
70–79	6	6.4	2	1.5	8	3.5
80–89	1	2.6	3	3.8	4	3.4
90	1	17.7	0	0	1	4.1
Total	15	0.60	7	0.26	22	0.43
Age-adjusted		0.92		0.30		0.56
95% CI*		(0.4, 1.4)		(0.08, 0.5)		(0.3, 0.8)
Overall age- and sex-adjusted						0.57
95% CI*						(0.33–0.81)

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Table 2

Age- and Sex-Adjusted Average Annual Incidence Rates of Waldenström Macroglobulinemia per 100,000 Person-Years by Decade in Olmsted County, Minnesota, 1961 Through 2010

Decade	Male (n)	Female (n)	Total	Rate	95% CI
1961–1970	0	1	1	0.24	0.00–0.71
1971–1980	2	0	2	0.37	0.00–0.88
1981–1990	5	2	7	1.1	0.29–2.00
1991–2000	5	0	5	0.58	0.07–1.1
2001–2010	3	4	7	0.56	0.14–0.97
Total	15	7	22	0.57	0.33–0.81

Date and Age at Diagnosis with Status and Years of Follow-up of Waldenström Macroglobulinemia in Olmsted County, Minnesota 1961–2010

Table 3

Patient	Decade of diagnosis	Age at diagnosis	Gender	Years of follow-up	Status at follow-up
1	1961–1969	82	Female	0.03	Dead
2	1970–1979	72	Male	0.6	Dead
3	1970–1979	55	Male	0.6	Dead
4	1980–1989	71	Male	2.8	Dead
5	1980–1989	55	Male	9.0	Dead
6	1980–1989	94	Male	0.1	Dead
7	1980–1989	71	Male	3.4	Dead
8	1980–1989	53	Female	10.8	Dead
9	1980–1989	52	Female	13.7	Dead
10	1990–1999	58	Male	4.1	Dead
11	1990–1999	81	Male	0.2	Dead
12	1990–1999	50	Male	14.6	Dead
13	1990–1999	74	Male	7.9	Dead
14	1990–1999	78	Male	1.4	Dead
15	1990–1999	59	Male	17.8	Alive
16	2000–2010	73	Female	8.1	Dead
17	2000–2010	74	Female	8.4	Dead
18	2000–2010	77	Male	0.1	Dead
19	2000–2010	81	Female	2.1	Dead
20	2000–2010	52	Male	12.0	Alive
21	2000–2010	81	Female	10.4	Alive
22	2000–2010	51	Male	7.4	Alive