MAYO CLINIC

ORIGINAL ARTICLE

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

Robert A. Kyle, MD; Dirk R. Larson, MS; Ellen D. McPhail, MD; Terry M. Therneau, PhD; Angela Dispenzieri, MD; Shaji Kumar, MD; Prashant Kapoor, MD; James R. Cerhan, MD, PhD; and S. Vincent Rajkumar, MD

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% or more 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 WM, lymphoplasmacytic lymphoma with an IgG or IgA monoclonal protein, and those with an IgM monoclonal gammopathy of undetermined significance were excluded. The peripheral blood smears, bone marrow aspirates, and biopsy specimens 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 per 100,000 person-years (95% CI, 0.44-1.39 per 100,000 person-years) and for females was 0.30 per 100,000 person-years (95% CI, 0.08-0.53 per 100,000 person-years) with an age- and sex-adjusted incidence of 0.57 per 100,000 person-years (95% CI, 0.33-0.81 per 100,000 person-years). When evaluated using a smoothing spline, there was no convincing evidence for a change in the incidence of WM over the past 50 years. Patients diagnosed with WM after 2000 had an approximately 2-fold excess mortality compared with the expected population mortality (standardized mortality ratio, 2.4; 95% CI, 0.64-6.0).

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

 ■ Mayo Clin Proc. 2018;93(6):739-746

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 greater than 3 g/dL, but a specific level is not required for diagnosis. Waldenström macroglobulinemia is now recognized as a distinct clinical entity defined by the presence of a monoclonal IgM protein regardless of its size, 10% or more 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 WM (SWM) is defined as the presence of a serum monoclonal IgM protein of 3 g/dL or greater and/or 10% or more bone marrow lymphoplasmacytic infiltration but without evidence of

From the Division of Hematology (R.A.K., A.D., S.K., P.K., S.V.R.), Division of Biomedical Statistics and Informatics (D.R.L., T.M.T.), Division of Hematopathology (E.D.M.), and Division of Epidemiology (J.R.C.), Mayo Clinic, Rochester, MN.

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 level of 10 g/dL or less (to convert to g/L, multiply by 10.0), platelet count less than 100×10^9/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, 1270 cases of WM and 1060 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 per 100,000 person-years for WM, 0.3 per 100,000 person-years for LPL, and 0.6 per 100,000 person-years for WM and LPL combined. The WM/LPL incidence was higher in males (0.8 per 100,000 person-years) than females (0.4 per 100,000 person-years) and was highest in non-Hispanic whites, intermediate in non-Hispanic blacks, and lowest in Asian Pacific Islanders. In a Surveillance, Epidemiology, and End Results (SEER) analysis for 1988-2007, the age-adjusted incidence of WM was 0.38 per 100,000 person-years and was higher in men (0.54 per 100,000 person-years) than women (0.27 per 100,000 person-years).[7] Over that time frame, there was no statistically significant change in the incidence overall or by sex. Waldenström macroglobulinemia was not reportable to SEER registries prior to 1988. Phekoo et al[8] reported an age-adjusted (European standard population) incidence of 0.55 per 100,000 person-years for WM in South East England between 1999 and 2001. Iwanaga et al[9] reported an age-adjusted incidence (2000 US standard population) for WM/LPL of 0.065 per 100,000 person-years in Japan and 0.042 per 100,000 person-years in Taiwan from 1996 to 2003; rates in Japan were increasing over this time period but were stable for Taiwan.

The major source of epidemiological 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 (monoclonal gammopathy of undetermined significance [MGUS]) as well as patients with SWM potentially increasing the rate. Conversely, 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 be 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, Minnesota, and the surrounding Olmsted County has been provided almost exclusively by Mayo Clinic and Olmsted Medical Group, which includes the medical records for all Olmsted County patients. 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 that 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.

PATIENTS AND METHODS

Study Population

The records of all Olmsted County residents with a monoclonal IgM protein and bone marrow involvement by a lymphoproliferative

Mayo Clin Proc. ■ June 2018;93(6):739-746 ■ https://doi.org/10.1016/j.mayocp.2018.02.011
www.mayoclinicproceedings.org

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. Waldenström macroglobulinemia was defined as the presence of a monoclonal IgM protein of any size, 10% or more lymphoplasmacytic infiltration of the bone marrow, and the presence of anemia, constitutional symptoms, hyperviscosity, lymphadenopathy, or hepatosplenomegaly requiring therapy.[3,12] In cases in which 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 of 3 g/dL or greater and/or 10% or more 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 2 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, MGUS, SWM, or lymphoplasmacytic lymphoma with monoclonal IgG or IgA proteins were excluded. Only those persons who had lived in Olmsted County for at least 1 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 biopsy specimens, 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 morphology[13] and pattern of bone marrow involvement. Two-color flow cytometric immunophenotyping to assess the B-cell population had been performed previously in 11 cases using the following monoclonal antibodies: CD3, CD5, CD10, CD11c, CD16, CD19, CD20, CD22, CD23, CD45, CD14, and κ and λ immunoglobulin light chains. The antibodies to κ and λ light chains were obtained from Caltag/Invitrogen; all other antibody conjugates were from BD Biosciences. In addition, 6-color plasma cell flow cytometry had been performed previously in 2 cases using the following antibodies: CD19 PE-Cy7 (Clone SJ25C1; BD Biosciences), CD38 APC (Clone HB7; BD Biosciences), CD45 APC-H7 (Clone 2D1; BD Biosciences), CD138 Percp-Cy5.5 (Clone MI15; BD Biosciences), and κ and λ immunoglobulin light chains (both from Dako).[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 κ and λ 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 US decennial census population counts for Olmsted County as the denominators.[15] Age- and sex-adjusted incidence rates were calculated by direct standardization to the 2010 US population. We calculated 95% CIs for the incidence rates based on the Poisson distribution. Temporal trends in the incidence rates were examined using Poisson regression.

TABLE 1. Age- and Sex-Specific Incidence Rates of Waldenström Macroglobulinemia per 100,000 Person-Years in Olmsted County, Minnesota, 1961 Through 2010

Variable	Male		Female		Total	
	No.	Rate	No.	Rate	No.	Rate
Age (y)						
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 (95% CI)	…	0.92 (0.4-1.4)	…	0.30 (0.08-0.53)	…	0.56 (0.3-0.8)
Overall age- and sex-adjusted (95% CI)	…	…	…	…	…	0.57 (0.33-0.81)

RESULTS

We identified 22 patients who had WM diagnosed from January 1, 1961, to December 31, 2010. The median age at diagnosis was 71.5 years (range, 50-94 years). Males accounted for 68%, and whites constituted 95% of patients. The liver was palpable in one 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 g/dL). The value was 12 g/dL or less in 95%, while 57% had a hemoglobin value of 10 g/dL or less at diagnosis. The leukocyte counts ranged from 3.1 to 45.1 $\times$ 10^9/L (median, 6.9 $\times$ 10^9/L). The leukocytosis (leukocyte count, 45.1 $\times$ 10^9/L) in a single patient was due to WM, resolved quickly with chemotherapy, and did not recur. The platelet counts ranged from 49 $\times$ 10^9/L to 558 $\times$ 10^9/L with a median of 296 $\times$ 10^9/L. Thrombocytopenia (platelet count <150 $\times$ 10^9/L) was due to a packed bone marrow in 2 cases and without a recognized cause in 1, while in the 3 patients with platelet counts greater than 500 $\times$ 10^9/L, the increase was not related to a specific cause. The serum calcium concentration ranged from 8.4 to 12.1 mg/dL (to convert to mmol/L, multiply by 0.25). 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; to convert to μmol/L, multiply by 88.4). In the single patient with an elevated creatinine level greater than 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 (to convert to g/L, multiply by 10) at diagnosis. During the course of their disease, only 2 patients had an M component of less than 2.5 g/dL (0.5 and 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 κ in 9, λ in 5, and no monoclonal light chain in 2. Only 2 patients had an M protein level greater than 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 (κ, unmeasurable). One uninvolved serum immunoglobulin (IgA or IgG) was reduced in 9 of 15 (60%) 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 specimen was examined in 19 of the 22 (86%) patients, and the diagnosis of a lymphoplasmacytic lymphoma was confirmed. The bone marrow aspirate/biopsy specimens were not available for review in 3 patients, but the reports of the bone marrow examinations 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 contained 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 biopsy specimens, this infiltrate was present in a

Mayo Clin Proc. ■ June 2018;93(6):739-746 ■ https://doi.org/10.1016/j.mayocp.2018.02.011
www.mayoclinicproceedings.org

nodular, interstitial, and/or paratrabecular 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 2 cases. One case coexpressed CD5. Paraffin section immunohistochemistry performed on the bone marrow biopsy specimens 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 per 100,000 person-years (95% CI, 0.44-1.39 per 100,000 person-years) and for females was 0.30 per 100,000 person-years (95% CI, 0.08-0.53 per 100,000 person-years). The age- and sex-adjusted annual incidence rate for WM was 0.57 per 100,000 person-years (95% CI, 0.33-0.81 per 100,000 person-years) (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; other causes included myelodysplasia in 3, WM/lymphoma in 3, stroke in 2, congestive heart failure from doxorubicin toxicity in 1, and upper gastrointestinal tract hemorrhage in 1. 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 status of all 22 patients are provided in Table 3. Over the entire period, patients with WM had a 5-fold excess mortality (standardized mortality ratio, 5.4; 95% CI, 3.2-8.5), although mortality was much lower for patients diagnosed after 2000 (standardized mortality ratio, 2.4; 95% CI, 0.64-6.0).

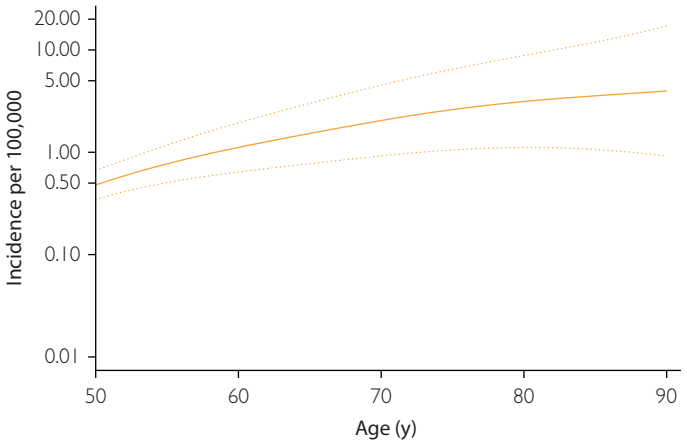

FIGURE 1. Age- and sex-adjusted incidence rates of Waldenström macroglobulinemia per 100,000 person-years in Olmsted County, Minnesota, 1961 through 2010. Dotted lines represent 95% CIs.

DISCUSSION

In 1944, Jan Waldenström described 2 patients with oronasal bleeding, normochromic anemia, elevated erythrocyte sedimentation rate, and lymphadenopathy.[16] This entity, later termed *Waldenström macroglobulinemia*, is a well-recognized lymphoplasmacytic 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 person-years based on a long-term study in a stable, geographically well-identified population. Similar to our previous studies on the incidence of multiple myeloma,[17] the region studied is well-suited for this purpose because of excellent case ascertainment and high-quality medical care. Our results are consistent with other US epidemiological studies that have been reported utilizing the SEER data. Groves

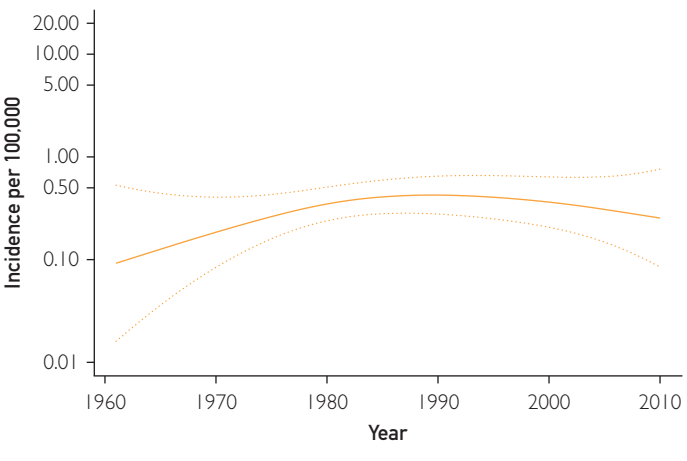

FIGURE 2. Age- and sex-adjusted incidence rates of Waldenström macroglobulinemia per 100,000 person-years in Olmsted County, Minnesota, by decade, 1961 through 2010. Dotted lines represent 95% CIs.

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 (No.)	Female(No.)	Total (No.)	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

et al[10] reported a rate of 0.34 per 100,000 person-years in males and 0.17 per 100,000 person-years in females. Similar results of 0.38 per 100,000 person-years were reported by Wang et al[7] utilizing SEER data. The rates in men were higher (0.54 per 100,000 person-years) than in women (0.27 per100,000 person-years). The age-adjusted incidence (2000 US standard population) from 2011-2012 was 0.3 per 100,000 person-years for WM, 0.3 per 100,000 person-years for LPL, and 0.6 per 100,000 person-years for WM and LPL combined. In the United Kingdom, Phekoo et al[8] found a rate of 0.55 per 100,000 population per year in the South Thames Haematology Registry in South East England.

In our study, to ensure complete case ascertainment, we reviewed the medical 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 serum protein electrophoresis and immunoelectrophoresis or immunofixation at Mayo Clinic. We were careful to exclude patients with other lymphoproliferative disorders as well as SWM 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

TABLE 3. Date and Age at Diagnosis With Survival Status and Years of Follow-up of Patients With Waldenström Macroglobulinemia in Olmsted County, Minnesota, 1961-2010

Patient	Decade of diagnosis	Age (y) at diagnosis	Sex	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

Mayo Clin Proc. ■ June 2018;93(6):739-746 ■ https://doi.org/10.1016/j.mayocp.2018.02.011
www.mayoclinicproceedings.org

with great precision. Virtually all residents of Olmsted County seek their medical care at Mayo Clinic or 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 sex distribution of our patients with WM 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 one case, has also been previously described.

Our study results reveal that the incidence of WM has remained virtually stable over a long period of time. More importantly, we found that WM is a very rare disorder with an incidence of approximately 0.6 per 100,000 person-years. 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 WM.[2] However, this change will convert most if not all cases of IgM MGUS into WM, making it one of the more common malignancies in the world. This scenario highlights how population-based incidence estimates are susceptible to increases of 100-fold or larger due not to a real increase but 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 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] because their risk of progression is low and overall survival has been found to be similar to that of the general population.[19,20] This rate is severalfold lower than the incidence of multiple myeloma, a closely related plasma cell malignancy.

CONCLUSION

This study is the first epidemiological 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 severalfold lower than that of multiple myeloma. The incidence of this disease has not changed during the past half century.

Abbreviations and Acronyms: **LPL** = lymphoplasmacytic lymphoma; **MGUS** = monoclonal gammopathy of undetermined significance; **SEER** = Surveillance, Epidemiology, and End Results; **SWM** = smoldering Waldenström macroglobulinemia; **WM** = Waldenström macroglobulinemia

Grant Support: This work was supported in part by research grants CA107476, CA168762, and CA186781 from the National Cancer Institute. The study was made possible by the Rochester Epidemiology Project (grant number R01-AG034676; Principal Investigators: Walter A. Rocca, MD, MPH, and Jennifer L. St Sauver, PhD).

Potential Competing Interests: Dr Dispenzieri has received grants from Takeda Pharmaceutical Company Limited, Pfizer Inc, Prothena Corporation plc, Celgene Corporation, and Alnylam Pharmaceuticals, Inc. Dr Kumar has received research grants/funding to institution for clinical trials from AbbVie Inc, Celgene Corporation, Janssen Pharmaceuticals, Inc, Kite Pharma, Merck & Co, Inc, Novartis AG, Roche Pharma, Sanofi, and Takeda Pharmaceutical Company Limited and has served on the advisory boards of AbbVie Inc, Celgene Corporation, Janssen Pharmaceuticals, Inc, Kite Pharma, Merck & Co, Inc, Oncopeptides AB, and Takeda Pharmaceutical Company Limited. The rest of the authors report no potential competing interests.

Correspondence: Address to Robert A. Kyle, MD, Division of Hematology, Mayo Clinic, 200 First St SW, Rochester, MN 55905 (kyle.robert@mayo.edu).

REFERENCES

1. King RL, Gonsalves WI, Ansell SM, et al. Lymphoplasmacytic lymphoma with a non-IgM paraprotein shows clinical and pathologic heterogeneity and May Harbor *MYD88* L265P mutations. *Am J Clin Pathol*. 2016;145(6):843-851.
2. Owen RG, Treon SP, Al-Katib A, et al. Clinicopathological definition of Waldenstrom's macroglobulinemia: consensus panel recommendations from the Second International Workshop on Waldenstrom's Macroglobulinemia. *Semin Oncol*. 2003; 30(2):110-115.
3. Kyle RA, Rajkumar SV. Criteria for diagnosis, staging, risk stratification and response assessment of multiple myeloma

[published correction appears in *Leukemia*. 2014;28(4):980]. *Leukemia*. 2009;23(1):3-9.

4. Kyle RA, Treon SP, Alexanian R, et al. Prognostic markers and criteria to initiate therapy in Waldenstrom's macroglobulinemia: consensus panel recommendations from the Second International Workshop on Waldenstrom's Macroglobulinemia. *Semin Oncol*. 2003;30(2):116-120.
5. Kyle RA, Benson JT, Larson DR, et al. Progression in smoldering Waldenstrom macroglobulinemia: long-term results. *Blood*. 2012;119(19):4462-4466.
6. Teras LR, DeSantis CE, Cerhan JR, Morton LM, Jemal A, Flowers CR. 2016 US lymphoid malignancy statistics by World Health Organization subtypes. *CA Cancer J Clin*. 2016;66(6):443-459.
7. Wang H, Chen Y, Li F, et al. Temporal and geographic variations of Waldenstrom macroglobulinemia incidence: a large population-based study. *Cancer*. 2012;118(15):3793-3800.
8. Phekoo KJ, Jack RH, Davies E, Møller H, Schey SA; South Thames Haematology Specialist Committee. The incidence and survival of Waldenström's Macroglobulinaemia in South East England. *Leuk Res*. 2008;32(1):55-59.
9. Iwanaga M, Chiang CJ, Soda M, et al. Incidence of lymphoplasmacytic lymphoma/Waldenström's macroglobulinaemia in Japan and Taiwan population-based cancer registries, 1996-2003. *Int J Cancer*. 2014;134(1):174-180.
10. Groves FD, Travis LB, Devesa SS, Ries LA, Fraumeni JF Jr. Waldenström's macroglobulinemia: incidence patterns in the United States, 1988-1994. *Cancer*. 1998;82(6):1078-1081.
11. Rocca WA, Yawn BP, St Sauver JL, Grossardt BR, Melton LJ III. History of the Rochester Epidemiology Project: half a century of medical records linkage in a US population. *Mayo Clin Proc*. 2012;87(12):1202-1213.
12. Kapoor P, Ansell SM, Fonseca R, et al. Diagnosis and management of Waldenström macroglobulinemia: Mayo Stratification of Macroglobulinemia and Risk-Adapted Therapy (mSMART) Guidelines 2016. *JAMA Oncol*. 2017;3(9):1257-1265.
13. Remstein ED, Hanson CA, Kyle RA, Hodnefield JM, Kurtin PJ. Despite apparent morphologic and immunophenotypic heterogeneity, Waldenstrom's macroglobulinemia is consistently composed of cells along a morphologic continuum of small lymphocytes, plasmacytoid lymphocytes, and plasma cells. *Semin Oncol*. 2003;30(2):182-186.
14. Morice WG, Hanson CA, Kumar S, Frederick LA, Lesnick CE, Greipp PR. Novel multi-parameter flow cytometry sensitively detects phenotypically distinct plasma cell subsets in plasma cell proliferative disorders. *Leukemia*. 2007;21(9):2043-2046.
15. Kyle RA, Linos A, Beard CM, et al. Incidence and natural history of primary systemic amyloidosis in Olmsted County, Minnesota, 1950 through 1989. *Blood*. 1992;79(7):1817-1822.
16. Waldenström J. Incipient myelomatosis or «essential« hyperglobulinemia with fibrinogenopenia — a new syndrome? *Acta Med Scand*. 1944;117(3-4):216-247.
17. Kyle RA, Therneau TM, Rajkumar SV, Larson DR, Plevak MF, Melton LJ III. Incidence of multiple myeloma in Olmsted County, Minnesota: trend over 6 decades. *Cancer*. 2004;101(11):2667-2674.
18. Rajkumar SV, Dimopoulos MA, Palumbo A, et al. International Myeloma Working Group updated criteria for the diagnosis of multiple myeloma. *Lancet Oncol*. 2014;15(12):e538-e548.
19. Gobbi PG, Baldini L, Broglia C, et al. Prognostic validation of the international classification of immunoglobulin M gammopathies: a survival advantage for patients with immunoglobulin M monoclonal gammopathy of undetermined significance? *Clin Cancer Res*. 2005;11(5):1786-1790.
20. Rajkumar SV. Macro-quest. *Blood*. 2015;125(15):2318-2319.