Incidence of Waldenström’s Macroglobulinemia

By Lisa J. Herrinton and Noel S. Weiss

This study sought to determine the incidence and pattern of occurrence of Waldenström’s macroglobulinemia, a plasmacytoid lymphocyte malignancy that involves monoclonal production of the IgM M-component type. Cases with Waldenström’s macroglobulinemia have been reported since 1978 to the population-based cancer registry that serves western Washington state, and since 1988 to the eight other cancer registries that participate in the National Cancer Institute’s Surveillance, Epidemiology, and End-Results program. Persons less than 85 years old newly diagnosed with Waldenström’s macroglobulinemia were identified through 1989. The age-standardized annual incidence rate was 6.1 per million in white men and 2.5 per million in white women (1980 US standard). Only five cases were reported in black women, among whom the age-standardized annual incidence rate was 3.6 per million. No cases were reported among black men (5.8 cases expected, based on the rates in white men); this finding may be due to chance, underdiagnosis of Waldenström’s macroglobulinemia in this group, or may reflect a truly low rate. Further investigation of a large, racially diverse population is required to better characterize the epidemiology of this rare disease.

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WALDENSTRÖM’S macroglobulinemia is a malignancy involving proliferation of cells with lymphocyte and plasma cell characteristics with consequent monoclonal production of IgM.1 The disease occurs very infrequently, and its epidemiologic characteristics have not previously been reported. We conducted this study to estimate the incidence rate of Waldenström’s macroglobulinemia and to characterize its occurrence by age, sex, race, and time.

MATERIALS AND METHODS

Information obtained by the National Cancer Institute’s Surveillance, Epidemiology, and End-Results (SEER) program was used in this study. Since 1978, the western Washington Cancer Surveillance System, one of nine SEER areas, has sought to identify all persons newly diagnosed with Waldenström’s macroglobulinemia (histologic codes 9632, 1978 through 1987, and 9761, 1988 through 1989) in its surveillance area. The disease became reportable to the SEER program (histologic code 9761)2 in 1988. The remaining eight SEER areas include San Francisco-Oakland, CA; metropolitan Detroit, MI; metropolitan Atlanta, GA; and the states of Connecticut, Hawaii, Iowa, New Mexico, and Utah. Information was obtained through 1989, the most recent year for which SEER data were publicly available at the time that this study was undertaken.

Each registry in the SEER program reviews all cases of possible Waldenström’s macroglobulinemia and bases the final classification of indefinite cases on the expert judgment of a consulting pathologist. In the registry serving western Washington, among persons with a serum IgM spike and no radiologically demonstrable bone lesions, Waldenström’s macroglobulinemia is diagnosed if (1) there is plasmacytoid lymphocytic infiltration of bone marrow or lymph nodes, and (2) the patient has heparospomenegaly with hyperviscosity symptoms, coagulopathy, or cryoglobulinemia (R. Krierm, personal communication, January 1993). The cases in western Washington were reviewed by a single pathologist.

Estimates of the number of white and black men and women in each 5-year age group who were residents of each SEER surveillance area were available from SEER for the period 1978 through 1989. Age-standardized incidence rates were estimated separately for white and black men and women using the direct method, with 5-year age groups from the 1980 US population as the standard. Ninety-five percent confidence limits were approximated from the standard error of the log of the incidence rate for stratified data3 for whites and black women. No black men were identified as having Waldenström’s macroglobulinemia during the study period, and the investigators were not aware of a method to approximate the upper 95% confidence limit for stratified data with zero observations; thus, no upper confidence limit was estimated for this group.

RESULTS

There were 88 whites or blacks diagnosed as having Waldenström’s macroglobulinemia in western Washington and 63 diagnosed in the remaining SEER areas. In western Washington, the annual age-standardized incidence rate was 7.9 (95% confidence interval [CI] 5.5 to 11) per million in white men and 2.9 (95% CI, 1.8 to 4.5) per million in white women. Among men, the reported incidence increased from 1978-1981 through 1982-1985, but decreased somewhat thereafter (Table I). In women, there was a relatively low rate for the period 1982 through 1985, but no clear trend over the 12-year period.

In the eight other SEER locations, the annual incidence rates in white men and women were 4.9 (95% CI, 3.2 to 7.7) and 2.2 (95% CI, 1.3 to 3.6) per million, respectively. The annual age-standardized incidence rate for the nine SEER areas combined was 6.1 (95% CI, 4.4 to 8.2) per million in white men, 2.5 (95% CI, 1.7 to 3.5) per million in white women, and 3.6 (95% CI, 1.2 to 11) per million in black women (Table 2). No cases were reported in black men. Had the age-specific incidence rates in white men been present in the population of black men, 5.8 cases would have occurred. In whites, among whom there were enough cases to examine age-specific rates, incidence increased markedly with age; among men and women aged 80 to 84 years, the annual incidence was 41.9 and 16.7 per million, respectively (Table 2). The cumulative risk of the disease to age 84 years, ie, the probability that an individual was diagnosed...
Table 1. Age-Standardized Incidence (1980 US standard) of Waldenström's Macroglobulinemia

<table>
<thead>
<tr>
<th>Period</th>
<th>Men</th>
<th></th>
<th></th>
<th>Women</th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Calendar Period</td>
<td>N</td>
<td>Calendar Incidence Rate per Million</td>
<td>95% CI</td>
<td>N</td>
<td>Calendar Incidence Rate per Million</td>
</tr>
<tr>
<td>1978-81</td>
<td>13</td>
<td>5.7</td>
<td>2.2-15</td>
<td>11</td>
<td>3.7</td>
<td>1.9-7.0</td>
</tr>
<tr>
<td>1982-85</td>
<td>25</td>
<td>9.5</td>
<td>5.6-16</td>
<td>4</td>
<td>1.3</td>
<td>0.4-4.3</td>
</tr>
<tr>
<td>1986-89</td>
<td>21</td>
<td>7.6</td>
<td>4.3-13</td>
<td>12</td>
<td>3.4</td>
<td>1.8-6.4</td>
</tr>
</tbody>
</table>

In relation to calendar year, whites age ≤84 years, western Washington, 1978-1989.

with Waldenström's macroglobulinemia before age 85 years, was 421 and 171 per million in white men and women, respectively.

**DISCUSSION**

That no cases were reported among black men is of concern. One explanation is that Waldenström's macroglobulinemia was underreported or misdiagnosed more frequently in this group than in the other groups. This disease has clinical features in common with multiple myeloma (annual age-adjusted incidence rate among white men and women for the years 1985 through 1988, 84 and 58 per million, respectively), non-Hodgkin's lymphoma (294 and 198 per million, respectively), chronic lymphocytic leukemia, and monoclonal gammopathy of unknown significance, all of which occur much more frequently than Waldenström's macroglobulinemia. Indeed, it has been reported that only 25% of patients with IgM M components have Waldenström's macroglobulinemia.

The apparent increase in incidence among white men living in western Washington, as well as the higher rate in this location relative to the other eight SEER registries, may simply be caused by variability in ascertainment over time and geographic area of residence. Before concluding that the incidence of Waldenström's macroglobulinemia has increased during the period 1978 through 1989 in the United States, or that the western Washington population actually has a relatively high incidence of the disease, it would be necessary to explicitly evaluate this issue.

Epidemiologic studies of Waldenström's macroglobulinemia have not been reported. However, it has been suggested that IgM monoclonal gammopathy is a precursor of the disease. In a series of 242 Mayo Clinic patients with IgM monoclonal gammopathy, among whom diagnoses of malignancy or amyloidosis were initially ruled out, the risk of the occurrence of Waldenström's macroglobulinemia, as defined on the basis of an increase in the size of the serum IgM spike to 3.0 g/dL or more and an increase in lymphocytes or plasmacytoid lymphocytes in the bone marrow, averaged 1.3% per year. This was approximately 1,000-fold greater than the risk observed in the present study for a group with a similar age and sex distribution. While the criteria used to diagnose IgM monoclonal gammopathy and Waldenström's macroglobulinemia in the Mayo Clinic study differed from those used by SEER, the incidence of the malignancy among the clinic patients undoubtedly was elevated. Renier et al summarized 21 reports of families in which multiple cases were diagnosed, but the question of a

Table 2. Age-, Sex- and Race-Specific Incidence, and Age-Standardized Incidence (1980 US standard) of Waldenström's Macroglobulinemia

<table>
<thead>
<tr>
<th>Age Group (yr)</th>
<th>N at Risk (10^6)</th>
<th>Men Annual Incidence Rate per Million</th>
<th>95% CI</th>
<th>Women Annual Incidence Rate per Million</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>White</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≤29</td>
<td>0</td>
<td>14.7</td>
<td>—</td>
<td>0</td>
<td>14.0</td>
</tr>
<tr>
<td>30-39</td>
<td>2</td>
<td>5.49</td>
<td>0.4</td>
<td>2</td>
<td>5.36</td>
</tr>
<tr>
<td>40-49</td>
<td>2</td>
<td>3.85</td>
<td>0.5</td>
<td>1</td>
<td>3.81</td>
</tr>
<tr>
<td>50-59</td>
<td>17</td>
<td>2.86</td>
<td>5.9</td>
<td>5</td>
<td>2.95</td>
</tr>
<tr>
<td>60-69</td>
<td>24</td>
<td>2.46</td>
<td>9.8</td>
<td>14</td>
<td>2.79</td>
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<tr>
<td>70-79</td>
<td>36</td>
<td>1.40</td>
<td>25.7</td>
<td>20</td>
<td>1.98</td>
</tr>
<tr>
<td>80-84</td>
<td>13</td>
<td>0.31</td>
<td>41.9</td>
<td>10</td>
<td>0.60</td>
</tr>
<tr>
<td>Total</td>
<td>94</td>
<td></td>
<td></td>
<td></td>
<td>52</td>
</tr>
<tr>
<td>Age-standardized rate (95% CI)</td>
<td>6.1 (4.4-8.2)</td>
<td>2.5 (1.7-3.6)</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

| Black         |                 |                                     |        |                                        |        |
| ≤29           | 0               | 1.69                                | —      | 0                                      | 1.67   |
| 30-39         | 0               | 0.49                                | —      | 0                                      | 0.56   |
| 40-49         | 0               | 0.30                                | —      | 1                                      | 0.33   |
| 50-59         | 0               | 0.19                                | —      | 1                                      | 0.23   |
| 60-69         | 0               | 0.15                                | —      | 1                                      | 0.19   |
| 70-79         | 0               | 0.08                                | —      | 2                                      | 0.12   |
| 80-84         | 0               | 0.02                                | —      | 0                                      | 0.03   |
| Total         | 0               |                                     |        |                                        | 5      |
| Age-standardized rate (95% CI) | 0.0 (0.0-ND) | 3.6 (1.2-11) |


Abbreviation: ND, not determined.
heritable factor increasing risk for the disease has not been
evaluated in an epidemiologic study. There has also been a
report of three cases occurring in persons who had worked
as shoe repairers for 40 years or longer.9

A second look at the descriptive epidemiology of Walden-
ström’s macroglobulinemia would be appropriate in several
years’ time, after additional cases are identified in SEER
populations beyond western Washington. However, a better
understanding of the epidemiology of Waldenström’s mac-
roglobulinemia will await the results of studies of large, ra-
cially diverse populations in which ascertainment of this
rare disease is relatively complete.

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