Long-term Evaluation of Three Multiple-Case Waldenström Macroglobulinemia Families

Mary L. McMaster, Gyorgy Csako, Therese R. Giambarresi, Linda Vasquez, Melissa Berg, Stephanie Saddlemire, Benjamin Hulley, and Margaret A. Tucker

Abstract

Purpose: Because the clinical significance of immunoglobulin abnormalities reported in relatives of familial Waldenström macroglobulinemia (WM) patients is unknown, we initiated a follow-up study of three WM families originally evaluated 27 years previously.

Experimental Design: Of 29 eligible first-degree relatives of WM patients, 27 (93%) had originally participated in clinical and electrophoretic evaluations. We re-contacted all participants for prospective follow-up electrophoretic analysis and other studies.

Results: Initially, five relatives had IgM monoclonal gammopathy (IgM MG), and four had IgM polyclonal gammopathy (PG). Twenty-two relatives (81%) were re-evaluated. Median follow-up was 17 years (range, 7–27). At re-contact, all IgM MG persisted or progressed, including three that evolved to WM. Among the four with PG, two new IgM MG cases developed. Overall, seven relatives (26%) had IgM MG, and five (18%) had IgM PG.

Conclusions: Although based on small numbers, this study provides the longest comprehensive follow-up of WM families to date. IgM MG seems to be a phenotypic marker of WM susceptibility in some families and may have a high risk of progression to WM. IgM PG may also be important in WM families. These observations require validation in larger studies and, if confirmed, may be used to identify a cohort (relatives with IgM MG) for future prevention strategies.

Waldenström (or primary) macroglobulinemia (WM) is caused by the uncontrolled proliferation of lymphocytes and plasma cells associated with the production of a large IgM monoclonal protein. Despite the recognition of familial clustering of WM for many years (1–6), progress in understanding its scope and implications has been limited. In addition to reporting familial WM patients, several family-based studies have addressed characteristics of the relatives of these patients (1–4, 6, 7). These studies have documented various immunoglobulin abnormalities among blood relatives, including monoclonal gammopathy (MG), polyclonal gammopathy (PG), and decreased immunoglobulin levels. The MGs reported have been predominantly of the IgM type (IgM MG), suggesting that IgM MG may be part of the clinical spectrum of familial WM. Conversely, polyclonal changes have included all immunoglobulin types. Virtually all of these studies have been cross-sectional analyses, and follow-up data have been sparse. Therefore, it has been difficult to determine the clinical significance of these findings, including whether the observed abnormalities are transitory, persistent, or progressive, and if progressive, whether the rate of progression is different from that in the general population.

Three multiple-case WM families were referred to the National Cancer Institute for extensive evaluation during a 10-year period beginning in 1977. Because of our interest in understanding the long-term consequences of familial WM for relatives of WM patients and to further refine its phenotypic spectrum, we re-contacted each of these families for follow-up evaluation. We present here the results of the original evaluation and the subsequent longitudinal study spanning up to three decades.

Subjects and Methods

Patients. Three families were referred to the National Cancer Institute, NIH in the 1970s and 1980s following the diagnosis of WM in at least two patients in each family (Fig. 1). The study was conducted under Institutional Review Board approval, and all patients gave informed consent for sample collection and analysis according to current standards. All WM patients and their living first-degree relatives, as well as spouses of either patients or of patients’ relatives, were eligible to participate. First-degree relatives of patients found to have IgM MG were also eligible for the study. Among the three families, there were eight known cases of WM (termed index cases), of whom six were living at the time of referral. Among the first-degree relatives of WM patients, several family-based studies have addressed characteristics of the relatives of these patients (1–4, 6, 7). These studies have documented various immunoglobulin abnormalities among blood relatives, including monoclonal gammopathy (MG), polyclonal gammopathy (PG), and decreased immunoglobulin levels. The MGs reported have been predominantly of the IgM type (IgM MG), suggesting that IgM MG may be part of the clinical spectrum of familial WM. Conversely, polyclonal changes have included all immunoglobulin types. Virtually all of these studies have been cross-sectional analyses, and follow-up data have been sparse. Therefore, it has been difficult to determine the clinical significance of these findings, including whether the observed abnormalities are transitory, persistent, or progressive, and if progressive, whether the rate of progression is different from that in the general population.

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relatives of the index WM cases, there was a single known case of IgM MG in each of two families and a single case of non–Hodgkin lymphoma in one family. The diagnosis of WM was validated in seven of the eight index cases by review of the original pathology or autopsy report (n = 6, 75%), or by the referring physician’s report (n = 1, 16%). We were unable to obtain confirmatory records for one patient. Of 29 first-degree relatives alive at initial ascertainment, 27 (93%) consented to participate. Details of the initial evaluation of the original family (A), referred in 1977, have been published elsewhere (4). Pertinent features of all three families at initial ascertainment are presented in Table 1.

Methods. The scope of the current study was limited to the relatives of WM patients and applicable spousal controls. We evaluated all available living first-degree relatives of the eight index WM patients as well as participating non–bloodline spouses at NIH or in the field. At initial evaluation in the 1970s/1980s, participants provided serum and urine for electrophoretic analysis, blood for erythrocyte sedimentation rate (ESR), rheumatoid factor, and routine chemistry and hematology profiles, and serum for cryopreservation. Initial sample serum and urine electrophoresis and immunoelectrophoresis were done from 1977 to 1980 by Bio-Science (Columbia, MD) and subsequently through 1990.

In order to adjust for variations in methodologies and standardization across laboratories, crude IgM concentrations were converted to a percentage of the upper limit of the normal range (%ULN) reported by a given laboratory at the time of the assay. For the purpose of this study, IgM MG was defined as a monoclonal band identified as IgM by immunofixation electrophoresis (IFE) in agarose gel at the NIH Department of Laboratory Medicine and reviewed by one of the authors (G. Csako). Participants also underwent routine immunoglobulin quantitation by immunonephelometry. Because newer electrophoretic methods are more sensitive than those applied in the past (8), we retrieved archived serum during the re-contact phase whenever possible and did IFE to confirm the original immunoelectrophoresis results. Participants who were found to have a monoclonal IgM component with elevated quantitative IgM levels on screening were offered additional evaluation. Consenting patients underwent bone marrow aspiration and biopsy, which was reviewed by an experienced hematopathologist to determine whether the IgM MG was accompanied by an underlying lymphoproliferative process using morphologic and immunophenotypic WHO criteria (9). Patients with IgM MG who had no evidence of a lymphomatous process in the bone marrow or who declined bone marrow examination were categorized as having IgM MG of undetermined significance and were referred to their local physician for clinical follow-up.

Statistics. Data were classified according to a variable’s median and range when continuous, or absolute and relative frequencies when the variable was categorical. To account for possible familial effects, conditional logistic regression was used to test for the significance of differences in frequency of observations between relatives and unrelated

### Table 1. Characteristics at ascertainment of study subjects from three multiple-case WM families

<table>
<thead>
<tr>
<th></th>
<th>Index WM patients*</th>
<th>Relatives</th>
<th>Spouses</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total</td>
<td>8</td>
<td>27</td>
<td>23</td>
</tr>
<tr>
<td>Median age (range)</td>
<td>54 (36-69)</td>
<td>31 (16-80)</td>
<td>43 (24-67)</td>
</tr>
<tr>
<td>Sex</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>3 (38%)</td>
<td>16 (59%)</td>
<td>9 (39%)</td>
</tr>
<tr>
<td>Female</td>
<td>5 (62%)</td>
<td>11 (41%)</td>
<td>14 (61%)</td>
</tr>
<tr>
<td>Familial relationships</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>between/to</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>WM patients</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Parents</td>
<td>1 (12.5%)</td>
<td>1 (4%)</td>
<td>—</td>
</tr>
<tr>
<td>Siblings</td>
<td>5 (62.5%)</td>
<td>4 (15%)</td>
<td>—</td>
</tr>
<tr>
<td>Offspring</td>
<td>1 (12.5%)</td>
<td>20 (74%)</td>
<td>—</td>
</tr>
<tr>
<td>Complex</td>
<td>1 (12.5%)</td>
<td>2 (7%)</td>
<td>—</td>
</tr>
</tbody>
</table>

*WM patients who were diagnosed prior to referral of the family are termed “index WM patients” to distinguish them from patients diagnosed with WM during the study.

1 In the first column, the relationships between the index WM patients within the families are shown. The second column outlines the relationship of the relatives to the index WM or IgM MG patient(s) in their respective families.

Individual is both a parent and the offspring of other WM patients.

Individuals are both siblings and offspring of WM patients.

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**Fig. 1. Pedigree configurations of study participants from three multiple-case WM families at the time of ascertainment. The diagnoses indicated on these pedigrees represent conditions that were known to exist at presentation and do not include conditions that were detected during the initial evaluation or that developed during the follow-up period.**
spousal controls. We also computed significance tests using Fisher exact test because it is better suited for small samples. SAS (version 9.1) was used for computation. A two-sided \( P < 0.05 \) was considered statistically significant.

**Results**

Twenty participants were first-degree relatives of the index WM patients, and seven were first-degree relatives of the index IgM MG patients (Table 1). Among 27 total participating first-degree relatives, 22 \( (81\%) \) were available for follow-up. Reasons for nonparticipation in the follow-up study included death \( (n = 1) \), terminal illness \( (n = 1) \), voluntary withdrawal from follow-up \( (n = 1) \), and logistical obstacles \( (n = 2) \). Most members of family (A) had been evaluated on one additional occasion in the late 1980s, when families (B) and (C) were ascertained. Median follow-up duration was 17 years \( (range, 7-27) \).

Of the 23 spouse controls, 21 participated in the initial evaluation, and 2 more were enrolled during the re-contact phase. Controls were less likely than first-degree relatives to participate in follow-up. Of the 21 who participated initially, only 9 were available for follow-up with a median of 15 years \( (range, 2-28) \). Reasons for nonparticipation in the re-contact phase included loss-to-follow-up after divorce \( (n = 4) \), voluntary withdrawal from follow-up \( (n = 6) \), and logistical obstacles \( (n = 2) \).

**Immunoglobulin abnormalities in first-degree relatives of WM patients.** Immunoglobulin abnormalities documented in first-degree relatives during the study included IgM MG, PG of immunoglobulin types G, A, and M, and decreased immunoglobulin levels (Table 2). Although many abnormalities had already been present at the initial screening, additional abnormalities developed over time and were detected during follow-up evaluations. During the entire study period, there were 12 instances of different IgM abnormalities among 10 blood relatives. Among the 12 total occurrences of IgM abnormalities, 10 had at least one follow-up assay at intervals ranging from 1 to 18 years. In all 10 instances, an IgM aberration was again detected on subsequent assay(s). In contrast, there were six instances of polyclonal increases or decreases in IgG \( (n = 2) \) or IgA \( (n = 4) \) that occurred in five relatives who did not have a concurrent MG, and only two of these \( (both \text{ IgA PG}) \) were present at follow-up.

We observed IgM PG in at least two members of two families but in no members of the third family. The median age was 31 years \( (range, 19-37) \) at first detection of any polyclonal immunoglobulin abnormality and 35 years \( (range, 26-37) \) for IgM PG specifically. Of five individuals initially found to have IgM PG, two subjects \( (patients PM-6 and PM-7) \) later converted to IgM MG. In addition, as shown in Fig. 2A, one relative had persistent polyclonal IgM elevation over 18 years, one had a second elevated IgM level 10 years later, followed by a normal level at 27 years, and one declined follow-up.

Over the course of the study, we found MG in at least two members in each family. All MG was of the IgM type. IgM MG was more frequent in relatives of WM patients \( (n = 7) \) than in unrelated spouses \( (n = 2) \), but the difference was not significant. Among relatives, the median age at first detection of IgM MG was 52 years \( (range, 39-80) \). No patient with IgM MG had evidence of coincident rheumatic or autoimmune disease, allergy, or drug reaction. Among the seven individuals found to have IgM MG, four declined further evaluation with bone marrow aspiration and biopsy for various reasons, including serious concurrent unrelated medical illness \( (n = 2) \), concerns regarding potential implications for insurance coverage \( (n = 1) \), and patient refusal \( (n = 1) \). Table 3 summarizes the characteristics of all IgM MG patients through the time of their latest follow-up.

### Table 2. Frequency of electrophoretic and quantitative immunoglobulin abnormalities in 27 first-degree relatives of WM or IgM MG cases

<table>
<thead>
<tr>
<th>Immunoglobulin abnormality</th>
<th>At initial evaluation(^a)</th>
<th>At any evaluation(^b)</th>
</tr>
</thead>
<tbody>
<tr>
<td>First-degree relatives ( (n = 27) )</td>
<td>First-degree relatives ( (n = 27) )</td>
<td>Spouses ( (n = 23) )</td>
</tr>
<tr>
<td>Monoclonal immunoglobulin</td>
<td></td>
<td></td>
</tr>
<tr>
<td>IgM</td>
<td>5 ( (18%) )</td>
<td>7 ( (26%) )</td>
</tr>
<tr>
<td>IgG, IgA</td>
<td>0 ( (0%) )</td>
<td>0 ( (0%) )</td>
</tr>
<tr>
<td>Total polyclonal (^c)</td>
<td>( 7 ( (26%) )</td>
<td>11 ( (41%) )</td>
</tr>
<tr>
<td>Increased immunoglobulins</td>
<td>( 5 ( (18%) )</td>
<td>9 ( (33%) )</td>
</tr>
<tr>
<td>IgM</td>
<td>4 ( (15%) )</td>
<td>5 ( (18%) )</td>
</tr>
<tr>
<td>IgG, IgA</td>
<td>1 ( (4%) )</td>
<td>4 ( (15%)(^d) )</td>
</tr>
<tr>
<td>Decreased immunoglobulins</td>
<td>( 2 ( (7%))^(e)</td>
<td>2 ( (7%) )</td>
</tr>
<tr>
<td>IgM</td>
<td>0 ( (0%) )</td>
<td>0 ( (0%) )</td>
</tr>
<tr>
<td>IgG, IgA</td>
<td>2 ( (7%) )</td>
<td>2 ( (7%) )</td>
</tr>
</tbody>
</table>

\(^a\)The results in this column represent the cross-sectional findings from the initial evaluation time point. In contrast, the results in the next column represent the longitudinal findings over the entire duration of the study. The changes between columns illustrate how cross-sectional data may lead to an underestimate of the frequency of immunoglobulin abnormalities in WM families.

\(^b\)Data obtained over the entire study period were used to compare results between first-degree relatives and non-bloodline spouses. Observed differences between groups were not significant in all instances.

\(^c\)Total polyclonal abnormalities include both polyclonal increases and decreases. Polyclonal immunoglobulin changes are reported only for those first-degree relatives who did not have a concurrent IgM MG.

\(^d\)One relative had IgA PG \( (106\% \text{ ULN}) \) at initial evaluation that fluctuated slightly at 9 y \( (97\% \text{ ULN}) \) and 24 y \( (102\% \text{ ULN}) \). Another had a normal IgA level initially \( (76\% \text{ ULN}) \), then IgA PG at 10 y \( (121\% \text{ ULN}) \) and 24 y \( (112\% \text{ ULN}) \).

\(^e\)One relative had decreased IgG \( (32\% \text{ ULN}) \) at initial evaluation that did not persist at follow-up; subsequent levels were 54% ULN at 10 y and 57% ULN at 24 y. Another had decreased IgA \( (17\% \text{ ULN}) \) at initial evaluation that was normal \( (37\% \text{ ULN}) \) 10 y later.
of the bone marrow; however, biopsies of scalene lymph node and liver were negative, and no diagnosis was made. The patient's symptoms resolved spontaneously 6 weeks later, and he remained asymptomatic until our evaluation, when he presented with axillary lymphadenopathy, normal lymphocyte count, and an unequivocal serum IgM(κ) monoclonal component. Following the diagnosis of WM, patient M-1 returned to local medical care and remained untreated until his death 11 years later from complications of atherosclerotic coronary artery disease.

Patient M-2 had a history of IgM MG discovered during evaluation for new-onset erythema nodosum nearly 3 years prior to our screening. A serum electrophoresis done following resolution of the rash was unremarkable, and no further evaluation was attempted. At presentation for screening, the patient had an IgM(κ) monoclonal component. Bone marrow examination 2 months later provided a diagnosis of WM. At last re-contact, 26 years following diagnosis, the patient was alive with treated WM.

Patient M-3 had confirmation at screening of an IgM(κ) MG first documented by the patient's local physician 18 months earlier. In the absence of symptoms or physical or other laboratory findings, the patient declined bone marrow evaluation. He was followed with annual electrophoretic studies by his local physician. His IgM level fluctuated over time with a gradual upward trend, and he remained alive and asymptomatic with persistent IgM MG 16 years following ascertainment.

Two individuals (patients M-4 and M-5) were originally classified as having polyclonal IgM on the basis of their initial screening with serum electrophoresis. Upon re-contact 15 years later, patient M-4 was discovered to have an IgM(λ) MG. An IFE done using archived serum retrieved from patient M-4's first visit showed a monoclonal IgM(λ) band whose mobility matched the band detected in the follow-up specimen. IgM concentration doubled over the 15-year interval. WM was diagnosed with bone marrow examination. At last follow-up, 25 months since diagnosis of WM, the patient remained untreated and asymptomatic with normal hematopoiesis and gradually increasing IgM levels.

Patient M-5 also had no detectable monoclonal band by electrophoresis at original screening. He was found to have an IgM(λ) MG as an isolated finding at the 15-year follow-up period, and IFE of archived serum identified an identical IgM(λ) band. The patient's IgM level had increased >2-fold during the 15-year interval. He remained asymptomatic with normal hematologic and other laboratory findings and declined bone marrow evaluation and additional follow-up.

During the period between ascertainment and re-contact, two blood relatives developed IgM MG. Patient PM-6 originally presented without symptoms, physical findings, or other laboratory abnormalities. At interim follow-up 11 years later, a minimal IgM PG had developed, along with increased IgC and IgA, in the context of HIV infection. At re-contact, 16 years after detection of the PG, an IgM(κ) MG had emerged, along with urinary excretion of free κ light chains and elevated creatinine. All other laboratory values were normal. The patient declined bone marrow examination. Subsequent follow-up IFE 8 months later documented persistent IgM(κ) MG of undetermined significance with a moderate increase in IgM. The patient's health status remained stable, with normal hematologic variables.

**Course of IgM MG in first-degree relatives of WM patients.** The temporal course of the blood relatives found to have IgM MG is depicted in Fig. 2B. In addition to the two blood relatives whose IgM MG evolved from IgM PG, five other relatives were found to have IgM MG at initial screening. Among these, two individuals (patients M-1 and M-2) had IgM levels >600% ULN and were diagnosed with WM following bone marrow examination done within 2 months of initial screening. Interestingly, patient M-1 had been evaluated 8 years earlier for fever, night sweats, weight loss, and mild lymphocytosis. Serum electrophoresis showed elevated α1- and α2-globulin fractions compatible with an acute phase reaction, but was otherwise unremarkable. Mature lymphocytes comprised 30% of the bone marrow; however, biopsies of scalene lymph node and liver were negative, and no diagnosis was made. The patient's symptoms resolved spontaneously 6 weeks later, and he remained asymptomatic until our evaluation, when he presented with axillary lymphadenopathy, normal lymphocyte count, and an unequivocal serum IgM(κ) monoclonal component. Following the diagnosis of WM, patient M-1 returned to local medical care and remained untreated until his death 11 years later from complications of atherosclerotic coronary artery disease.

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**Fig. 2.** Course of first-degree relatives of WM patients who were found to have IgM abnormalities during the study period. **A** and **B,** IgM levels were expressed as %ULN for the given reporting laboratory. **A,** three relatives had polyclonal IgM elevations. Patient P-1 had sustained IgM PG at every evaluation over 19 y. Patient P-2 was not available for follow-up. Patient P-3 had modest increases of IgM at original evaluation and at 10 yr but sustained normal levels at re-contact. **B,** seven relatives had IgM MG at original evaluation (n = 5) or had developed it at re-contact (n = 2). Patients M-1 to M-3 were diagnosed with IgM MG at initial screening. At original evaluation, patients M-4 and M-5 had IgM MG that was initially misdiagnosed as IgM PG. Patients PM-6 and PM-7 were originally found to have IgM PG, which was confirmed by IFE of serum stored from their original evaluation; they both later developed IgM MG, which was detected at the evaluation (*). Arrows, the points at which patients M-1, M-2, and M-4 were diagnosed with WM. For patient M-2, the decline in IgM concentration coincided with response to treatment.
Ten months prior to presentation, patient PM-7 was diagnosed with node-based stage IA non–Hodgkin lymphoma (diffuse histiocytic subtype) and was treated successfully with excision and combination chemotherapy. At initial screening, his examination and laboratory findings were normal with the exception of an IgM PG. The polyclonal nature of the IgM elevation was confirmed by IFE of archived original serum at the time of re-contact. On follow-up at 17 years, a new IgM(M) MG was identified, accompanied by a 55% increase in IgM level. Persistence of the IgM MG was confirmed 1 year later. The patient deferred bone marrow examination and remained otherwise healthy without evidence of lymphoma recurrence.

**Immunoglobulin abnormalities in spousal controls.** Polyclonal immunoglobulin changes were found in six instances among five spouse controls, including three controls with IgM PG at 176% ULN, 148% ULN, and 129% ULN, respectively. All three with IgM PG were spouses within a single family, and none had IgM MG by IFE of archived serum. We were unable to assess the course of IgM PG in single family, and none had IgM MG by IFE of archived serum. For one of these spouses, the IgM band could be detected by IFE in only one sample 16 years later. His IgM level was normal initially and at follow-up. For the other control, who was not available for follow-up, there was sufficient archived serum for only one IFE, which detected a weak IgM MG with normal IgM levels.

**Table 3. Characteristics of patients found to have IgM-MG**

<table>
<thead>
<tr>
<th>Patient</th>
<th>Sex</th>
<th>At time IgM MG first detected</th>
<th>Abnormal Lab*</th>
<th>Serum electrophoresis result</th>
<th>Vital status</th>
<th>Disease status</th>
<th>At last follow-up</th>
<th>Abnormal Lab</th>
<th>Time (mo), WM</th>
<th>Death or last follow-up</th>
</tr>
</thead>
<tbody>
<tr>
<td>M-1</td>
<td>M</td>
<td>80</td>
<td>+</td>
<td>IFE</td>
<td>D</td>
<td>WM, untreated</td>
<td>n.d.</td>
<td>n.d.</td>
<td>1</td>
<td>143</td>
</tr>
<tr>
<td>M-2</td>
<td>F</td>
<td>57</td>
<td>-</td>
<td>IFE</td>
<td>A</td>
<td>WM, treated</td>
<td>IgM(M)</td>
<td>IgG</td>
<td>35</td>
<td>321</td>
</tr>
<tr>
<td>M-3</td>
<td>M</td>
<td>60</td>
<td>-</td>
<td>IFE</td>
<td>A</td>
<td>IgM MG, persistent</td>
<td>IgM(M)</td>
<td>IgG</td>
<td>n.a.</td>
<td>199</td>
</tr>
<tr>
<td>M-4</td>
<td>M</td>
<td>41</td>
<td>-</td>
<td>IFE</td>
<td>A</td>
<td>IgM MG, IgM(M)</td>
<td>IgM(M)</td>
<td>n.a.</td>
<td>192</td>
<td>217</td>
</tr>
<tr>
<td>M-5</td>
<td>M</td>
<td>39</td>
<td>-</td>
<td>IFE</td>
<td>A</td>
<td>IgM MG, progressive</td>
<td>IgM(M)</td>
<td>IgM(M)</td>
<td>n.a.</td>
<td>184</td>
</tr>
<tr>
<td>PM-6</td>
<td>M</td>
<td>52</td>
<td>+↑</td>
<td>+RF</td>
<td>A</td>
<td>IgM MG, progressive</td>
<td>IgM(M)</td>
<td>n.a.</td>
<td>8</td>
<td>8</td>
</tr>
<tr>
<td>PM-7</td>
<td>M</td>
<td>52</td>
<td>+↑</td>
<td>+RF</td>
<td>A</td>
<td>IgM MG, progressive</td>
<td>IgM(M)</td>
<td>n.a.</td>
<td>16</td>
<td>16</td>
</tr>
</tbody>
</table>

Abbreviations: mo, months; S/S, signs and/or symptoms; Lab, laboratory studies; (-), none; (+), present; ↑, increased; ↓, decreased; A, alive; D, dead; RF, rheumatoid factor; BJ, Bence-Jones proteinuria; n.d., not done; n.a., not applicable.

*Laboratory studies included serum and urine EP/IEP/IFE; serum chemistries, ESR, RF, complete blood counts, and (since 2000) serum β2-microglobulin (β2M).

Symptoms consisted of fatigue and weight loss in the presence of HIV infection.

**Discussion**

Longitudinal studies are needed to better understand the development of familial WM, as well as IgM MG and its relationship to WM. Earlier family studies provided little indication of the clinical significance of immunoglobulin abnormalities in relatives of WM patients, although one report (3) suggested that the risk of progression is high. Unfortunately, it is very challenging to conduct long-term family studies, and therefore virtually all published family studies have been cross-sectional. We have presented here the first report describing a nearly 30-year follow-up of three well-characterized WM families.

Monoclonal IgM gammopathy is uncommon in the general population. Its prevalence overall is estimated to be ~0.5%, and it is estimated to account for only 5% to 30% of all MG in various populations (10–13). In contrast, MG was observed in nearly 20% of first-degree relatives in this study and was exclusively of the IgM type. Thus, the frequency of IgM MG among relatives of WM patients in these families was increased >30-fold higher than expected. Although earlier studies identified a high frequency of IgM MG in first-degree relatives (1, 3, 14, 15), the affected proportions were smaller than in our families (16). This may be due in part to the increasing sensitivity of screening methods over time. Whereas immunoelectrophoresis is relatively sensitive for the detection of IgM MG in most cases, IFE is more sensitive for the detection of IgM MG at low concentrations (17–20). Thus, studies conducted prior to the general availability of IFE might be expected to have detected a smaller proportion of IgM MG upon screening of WM family members. This expectation is consistent with our observations for patients M-3 and M-4, for whom immunoelectrophoresis...
failed to identify an IgM MG that was subsequently detected by IFE. However, some bands identified by IFE, particularly those found at the lower detection limit, may not be clinically relevant (21), underscoring the need for longitudinal follow-up studies. In the current study, the monoclonal band was accompanied by an elevated IgM level in all of the affected relatives. In contrast, in the two spouses with IgM MG, the IgM level was normal. Furthermore, among affected relatives, IgM MG was either persistent or progressive in every instance. Thus, IgM MG, especially in the presence of an elevated IgM level, seems to be a strong phenotypic marker of susceptibility in familial WM.

The two individuals who developed IgM MG during the course of the study merit additional comment. In one subject, IgM MG evolved from a PG associated with HIV infection. IgM MG occurs in association with HIV in ~0.1% of HIV-positive patients (22). To date, there has been only one report of WM developing in an HIV-positive individual (23), which may reflect the poor long-term survival of HIV patients in the pre-highly active antiretroviral therapy era. Nonetheless, HIV-related IgM MG seems to be a rare occurrence. The relative contributions of genetic susceptibility and environmental exposure in our patient with HIV are unknown.

The other individual developed IgM MG following successful treatment of a previous stage I non–Hodgkin lymphoma. Both population and clinicopathologic studies indicate some familial overlap among B cell tumors in general (24–26). These findings suggest shared genetic susceptibility among these disorders. No population studies address familial risk estimates for WM specifically. However, a recent study found evidence for cross-susceptibility between lymphoplasmacytic lymphoma (the histopathologic correlate of WM) and all non–Hodgkin lymphoma and chronic lymphocytic leukemia, respectively (27). In a tertiary care–based series, 14% of familial WM patients reported a family history of a B cell malignancy other than WM (28), in contrast to a case-control study in which 5% of sporadic WM patients and 7% of controls reported a family history of hematolymphoproliferative malignancies (29). In addition, two recent genetic linkage analyses for WM (30) and Hodgkin lymphoma (31), respectively, found suggestive evidence for linkage within the same region on chromosome 4. Studies confirming these results are needed. However, in the aggregate, these data suggest that the familial WM phenotype may include other B cell neoplasms.

In this study, nearly half of the patients with IgM MG were subsequently diagnosed with WM. Two others had substantial increases in IgM levels during follow-up and continue to be at risk. Several recent studies have applied prognostic algorithms to predict the risk of conversion from sporadic IgM MG to WM (32–34) and have estimated a 15% to 25% probability of progression from IgM MG of undetermined significance to WM at 15 years. Of the seven first-degree relatives meeting the criteria for monoclonal gammopathy of undetermined significance in our families, only four also had adequate durations of follow-up to assess the rates of progression. Notably, two of four progressed to WM within 16 years. Although these numbers were small, the results suggest that the risk of progression could be higher in a familial context. This question may have important implications for relatives in WM families and should be explored further.

More problematic is the role of IgM PG in familial WM. In previous studies, polyclonal increases and decreases of any immunoglobulin were reported in 33.3% of first-degree relatives (16). IgM PG occurred as the sole abnormality in 10% of first-degree relatives in all studies combined. However, IgM PG was not a universal feature but instead was highly variable between families (6, 7). Although most authors suggested that the overall frequency seemed to be unusually high, there are no controlled studies that support the inclusion of IgM PG in the spectrum of familial WM. Polyclonal elevation of IgM is assumed to be more common than IgM MG in the general population, although its true population prevalence is not known except in certain subsets (e.g., HIV-positive patients). In this study, IgM PG was found in members from two of three families and was more common in family members than in spouses. However, our numbers were too small to detect meaningful differences. This finding may be due to chance or may reflect an effect of environmental exposures that both relatives and spouses have in common. It is noteworthy, however, that we documented the persistence of IgM PG in three of four relatives, and two later evolved an IgM MG. Larger longitudinal studies are needed to clarify this issue.

Several factors limit our study. First, small numbers curtailed our power to make statistical inferences. Second, our data are incomplete because we were unable to obtain follow-up data on all participants. Also, the intervals between data collection points were relatively long. Thus, we lack certain important information regarding precise onset, course, and rate of progression of IgM MG in family members. We plan to continue the follow-up of relatives with IgM MG to address this issue. Finally, these are highly selected, large families that may not be representative of all WM families. Despite these limitations, this study represents the longest and most comprehensive follow-up of familial WM to date and provides important information that enhances our developing understanding of familial WM. It is unique among family-based studies in terms of length of follow-up, completeness of family accrual and data collection, and inclusion of spousal controls.

In summary, these data suggest that IgM MG may be an important phenotypic marker of genetic susceptibility in WM families. This hypothesis is consistent with a recent report that evidence for genetic linkage is strengthened by the inclusion of IgM MG in the familial WM phenotype (30) and has important implications for future genetic studies. Our findings also raise the possibility that polyclonal IgM elevations may be another important feature of the phenotype in these families, although further studies are needed to confirm this observation. Our results further suggest that IgM MG in WM families may be more likely to progress to WM, compared with its course in the general population. Whether the rate of progression is altered in the familial setting is a question still subject to further clarification; however, it is notable that nearly half of the relatives with IgM MG were diagnosed with WM within 16 years. Finally, if this observation is confirmed, then we have identified a group of high-risk individuals as candidates for WM prevention strategies in the future.

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Long-term Evaluation of Three Multiple-Case Waldenström Macroglobulinemia Families

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