ABSTRACT

Purpose: To verify the reliability of the new criteria for the diagnosis of IgM gammopathies recently proposed by an international panel of experts (Athens, 2002).

Experimental Design: A retrospective series of 698 patients with IgM gammopathy was reviewed paying attention to symptoms, serum IgM concentration, bone marrow infiltration, blood cell count and clinical course. Four clinical entities can be identified: IgM monoclonal gammopathy of undetermined significance (IgM-MGUS), asymptomatic and symptomatic Wandenstro¨m's macroglobulinemia (A-WM and S-WM, respectively), and IgM-related disorders, although this last was excluded from the study because of the scarcity of patients due to probable selection biases. The observed mortality was studied related to that expected in the general population of comparable age and sex and over an equivalent period of follow-up (standardized mortality ratio, SMR).

Results: IgM-MGUS, A-WM, and S-WM shared many clinical aspects but, with respect to the general population, patients with IgM-MGUS had a slight but definite survival advantage, those with A-WM had a mortality rate equivalent to that of the general population, whereas the SMR of patients with S-WM was 5.4. Within A-WM and S-WM the SMR values did not vary significantly in relation to marrow lymphocyte counts or serum IgM concentrations.

Conclusions: Our findings represent a prognostic validation of the applied diagnostic criteria for three of the four identifiable clinical entities and highlight the importance of symptoms over serum IgM concentration and marrow infiltration.

INTRODUCTION

In the Second International Workshop on Waldenström's macroglobulinemia held in Athens, Greece, in September 2002, a consensus panel of experts tried to define clear and reproducible criteria for the diagnosis of the clinicopathologic entities recognizable within the spectrum of IgM gammopathies (1). It was stated that Waldenström's macroglobulinemia is characterized by "unequivocal evidence of bone marrow infiltration by lymphoplasmacytic lymphoma, irrespective of the serum IgM concentration." Moreover, Waldenström's macroglobulinemia should be considered symptomatic (S-WM) or asymptomatic (A-WM) according to the presence or absence of features attributable to tumor infiltration, for example, constitutional symptoms, cytopenia(s), organomegaly, and/or symptoms attributable to the monoclonal protein (hyperviscosity syndrome, cryoglobulinemia, amyloidosis, or autoimmune phenomena such as peripheral neuropathy and cold agglutinin disease). The clinical condition with symptoms attributable to the IgM monoclonal protein, but without overt evidence of lymphoma, was recognized as a distinct entity for which the term "IgM-related disorders" was proposed. Finally, patients with IgM monoclonal gammopathy but no morphologic evidence of bone marrow infiltration by lymphoma (or even equivocal marrow infiltrates without confirmatory phenotypic studies) should be classified as having a monoclonal gammopathy of undetermined significance (IgM-MGUS).

This classification seems to be clinically adequate and acceptable but is yet to be widely applied. Here we present how the new clinical criteria classified our large series of patients with IgM monoclonal component and the main clinical and prognostic characteristics of the subgroups thus identified.

Furthermore, because some of us (2) had recorded a distinct mortality increase (4.8 times higher than in the general population) in a recent study on Waldenström's macroglobulinemia we were particularly interested in evaluating the true prognostic impact of each clinicopathologic entity through estimates of how much mortality in each subgroup differs from that in the general population.
The IgM-related disorder cases were not considered in this study for two reasons: first, probably as a result of selection biases there were too few such cases in our series—only 14 patients were allocated in this category in comparison with the 698 diagnosed in the other groups; second, the clinical heterogeneity of the IgM-related disorder group is substantial in relation to the variable proportion of the underlying different nonlymphomatous disorders supporting monoclonal IgM, and this heterogeneity can hamper the identification of constitutive clinical characteristics.

PATIENTS AND METHODS

Patients. Data from retrospective series of patients with IgM gammopathy diagnosed and followed up in several cooperating centers were collected and pooled. The above-mentioned diagnostic criteria by Owen et al. (1) were applied to these patients. IgM producing diseases different from true, idiopathic IgM gammopathies were excluded (IgM multiple myelomas, low-grade B-cell non-Hodgkin lymphomas other than the lymphoplasmacytic type, non-Hodgkin lymphomas in leukemic phase, i.e., with clonal lymphocytes \(>5.0 \times 10^9/L\), heavy-chain diseases). Moreover, because patients with IgM monoclonal gammopathy due to hepatitis C virus–related cryoglobulinemias, peripheral neuropathy, amyloidosis, rheumatic disorders and autoimmune diseases (i.e., those collected in the IgM-related disorder category) were more often seen by specialists other than the hematologists and oncologists of the cooperating centers, such cases (14 in all) were excluded from the study to avoid selection biases. Thus, there were 698 patients eligible for this study who were observed from January 1, 1978, to December 31, 2002. The median follow-up was 64 months (range, 2–281). Besides clinical history and physical examination, diagnostic procedures included laboratory investigations (blood cell count, liver and renal function, serum and urine protein quantification, serum and urine electrophoresis, densitometric determination of IgM concentration, and serum and urine immunofixation), bone marrow trephine and/or aspiration, standard chest X-ray, and upper abdomen ultrasonography.

Bone marrow infiltration was quantified as percent of the total amount of nucleated cells preferably on a bone marrow biopsy; in patients in whom marrow biopsy had not been done, data from marrow aspiration were accepted. Apart from the morphologic features of bone marrow lymphocytes, which had to show plasmacytoid differentiation or characteristic immunophenotypic profiles (CD19+, CD20+, CD22+, CD79+) to meet the diagnostic requirement for Waldenström's macroglobulinemia, in patients with incomplete or absent immunophenotypic studies a level of \(>10\%\) of lymphoid cells was considered as a suitable cutoff for “unequivocal evidence of marrow infiltration,” whereas a level of bone marrow lymphocytes \(\leq 10\%\) was categorized as “no evidence of lymphoma infiltration.” This cutoff is consistent with our previous data collected from patients who had both immunophenotypic investigations and quantitative evaluations of lymphoplasmacytic infiltration and, moreover, matches with the methods applied by Kyle et al. (3).

Patients with IgM-MGUS and A-WM were followed up with a “watch and wait” policy, without specific therapy for their gammopathy. All patients with S-WM were treated and the majority received chlorambucil-based regimens. Twenty-seven subjects were treated with cyclophosphamide–vincristine–prednisone–like drug combinations and three with fludarabine schedules. Mortality among the treated patients was not differentiated into either disease- or treatment-related or otherwise because the complex course and variable clinical manifestations of S-WM make such a discrimination potentially inaccurate and a source of several biases.

Statistics. Comparisons of means were done with the \(t\) test for unpaired cases (4). Overall survival from the date of diagnosis to death from any cause was the only time parameter considered to exclude any bias in attributing death directly or indirectly to IgM gammopathy, age-related comorbidity, or treatment itself, if any. The purpose was to examine, as a whole, how much the presence of an IgM gammopathy, classified according to the different clinical entities into which such a condition can be divided, affected patients’ mortality in comparison with the mortality observed in the general population. Overall survival was evaluated by the Kaplan and Meier method (5) in the population of patients and, necessarily, by the life-table method (6), with 1-year intervals, in the general population. The age-, gender-, and calendar year–specific death rates available from the national Italian mortality tables were used to calculate the expected deaths in subjects of the same sex and same age in the calendar year of first observation, taking into account that age changed according to individual birthdays in every year of the follow-up period. For example, the expected probability of death (available from the Italian mortality tables) of a man born on August 1, 1926, who survived the whole of 1997 is that of a 70-year-old man during the first 212 days of the year (i.e., 0.03063 per 100,000) and that of a 71-year-old man in the remaining 153 days (i.e., 0.03376 per 100,000); the resulting probability of death during the whole of 1997 will be 0.03063 \(\times\) 212 / 365 + 0.03376 \(\times\) 153/365 = 0.03194. In this way, each patient was considered to have a wide control from the general population with corresponding sex, age, and follow-up period, with a well-defined probability of dying. The reference to the national mortality tables was possible because minimal mortality differences have been observed among people from single regions. The sum of the observed deaths (those recorded in the population of patients) and the sum of the expected deaths (those obtained from mortality table data) were used to determine the standardized mortality ratio (SMR), calculated as the ratio of observed to expected deaths from any cause.

Moreover, it was possible to calculate and compare the curves of the observed cumulative survival probability of the patients with the expected survival probability of the general population and to apply standard inference techniques to the obtained SMR (95% confidence limits and continuity-corrected \(\chi^2\) test; ref. 7).

RESULTS

Table 1 summarizes the main epidemiologic and clinical characteristics of the patients at diagnosis as classified according to the recommendations of the Athens Workshop. The three evaluated entities collected comparable numbers of patients whose basic clinical features were substantially similar concerning male/female ratio, age, duration of follow-up, light
Table 1  Epidemiologic and clinical characteristics of the patients at diagnosis according to the identified clinicopathologic entity (value range in parentheses)

<table>
<thead>
<tr>
<th></th>
<th>IgM-MGUS</th>
<th>A-WM</th>
<th>S-WM</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. of patients</td>
<td>207</td>
<td>217</td>
<td>274</td>
</tr>
<tr>
<td>Male/female ratio</td>
<td>1.46</td>
<td>1.49</td>
<td>1.25</td>
</tr>
<tr>
<td>Median age (y)</td>
<td>65.0 (29.9-89.3)</td>
<td>63.9 (35.8-88.1)</td>
<td>62.3 (24.9-91.6)</td>
</tr>
<tr>
<td>Marrow infiltration (%)</td>
<td>6.6 ± 2.2 (2-10)</td>
<td>26.0 ± 16.8* (11-92)</td>
<td>49.5 ± 22.8* (11-95)</td>
</tr>
<tr>
<td>Serum IgM (g/L)</td>
<td>8.8 ± 5.5 (1.1-45.0)</td>
<td>16.5 ± 10.9* (1.0-89.0)</td>
<td>26.9 ± 14.1* (2.7-89.3)</td>
</tr>
<tr>
<td>K/β ratio</td>
<td>3.1</td>
<td>3.4</td>
<td>3.3</td>
</tr>
<tr>
<td>Hemoglobin (g/L)</td>
<td>140 ± 15 (81-179)</td>
<td>134 ± 15 (87-163)</td>
<td>111 ± 23 (40-157)</td>
</tr>
<tr>
<td>Leukocytes (× 10^9/L)</td>
<td>6.8 ± 2.0 (1.6-13.1)</td>
<td>6.9 ± 1.9 (1.3-16.9)</td>
<td>7.0 ± 4.4 (1.5-29.0)</td>
</tr>
<tr>
<td>Platelets (× 10^9/L)</td>
<td>239 ± 89 (199-597)</td>
<td>236 ± 85 (121-577)</td>
<td>203 ± 96 (28-707)</td>
</tr>
<tr>
<td>Median follow-up (mo)</td>
<td>61 (4-242)</td>
<td>62 (2-228)</td>
<td>67 (2-281)</td>
</tr>
<tr>
<td>Observed/Expected deaths</td>
<td>9/21,232</td>
<td>30/21,806</td>
<td>152/28,135</td>
</tr>
<tr>
<td>SMR [95% confidence limits]</td>
<td>0.424 [0.194-0.804]</td>
<td>1.376 [0.928-1.964]</td>
<td>5.403 [4.578-6.336]</td>
</tr>
<tr>
<td>Person-years of observation</td>
<td>1066.1</td>
<td>1119.4</td>
<td>1536.7</td>
</tr>
</tbody>
</table>

*P < 0.001 for the difference from IgM-MGUS.

†P < 0.001 for the difference from A-WM.

The most remarkable results shown in the table are the very different SMRs of patients with the three clinicopathologic entities into which the patients were classified. Patients with A-WM showed a mortality rate very similar to that observed in the general reference population, whereas the group of patients with MGUS had less than half the number of deaths than that in the general population. In contrast, patients with S-WM had a more than five times higher mortality rate than that of the general population. Both these differences are statistically significant. These findings are supported by the considerable period of observation (more than 1,000 person-years of exposure to risk) and are graphically demonstrable by the comparison of cumulative survival of patients with that of the general population. Figure 1A shows that the survival curve of patients with MGUS actually remains higher than that of the general population for most of the follow-up period, and only in the last years—when the subjects at risk become very few—does the former curve approach the latter. The resulting SMR is significantly lower than expected. Figure 1B shows that the survival of patients with A-WM is very similar to, and statistically not different from, that expected in the general population, whereas Fig. 1C shows the marked reduction in survival of patients with S-WM in comparison with survival in the general population, with a statistically higher SMR than expected. Table 2 shows that differences in bone marrow lymphocyte infiltration or serum IgM concentration are not responsible for the substantial differences in SMR because splitting both patients with A-WM and S-WM into two subgroups according to levels of these two variables being either above or below the median cutoff limits produced only very slight variations in SMR.

**DISCUSSION**

Because the SMR represents a simple quantitative measurement of the impact that a disease ultimately has on the fate of patients, we decided to include it among a list of epidemiologic and clinical parameters to evaluate in order to validate the classification of nosologic entities recently recognized within the set of IgM gammapathies. We chose to avoid considering the disease-specific mortality of the patients because, for the purposes of this work, its comparison with mortality of the reference population would have been less meaningful both related to general deaths (from mortality tables) and related to the death-specific one (from tumor registries, if available). Moreover, discriminating causes of death in retrospective studies is too difficult and is open to criticism: many deaths can be questionably considered directly or indirectly related to the disease, or even fully independent of it.

The investigation on the IgM-related disorder group as it was recently defined (i.e., with symptoms attributable to the IgM monoclonal protein but without overt evidence of bone marrow infiltration; ref. 1) was abandoned in this study because we realized that a considerable number of patients potentially allocable to this group had been referred to specialists outside the cooperating centers (neurologists, rheumatologists, and nephrologists). In the present series, however, many patients presenting symptoms due to the monoclonal protein (hyperviscosity syndrome, cryoglobulinemia, amyloidosis, peripheral neuropathy, cold agglutinin disease, etc.) were classified in the S-WM group based on clear marrow infiltration.

The main result of this study consists in the very different deviation of the observed from the expected survival in the three clinical entities evaluated. Indeed, the SMR seems to be the parameter that most strongly characterizes the three groups of patients because it shows a definite and statistically significant survival advantage for patients with IgM-MGUS, who had a mortality rate half of that in the general population, one third of that of the A-WM group, and more than one twelfth of that
of patients with S-WM. These last were the only patients with a significantly higher mortality than normal.

The interpretation of these findings is complex. Concerning the lower mortality of patients with MGUS, we believe that the presence of an intrinsically benign disorder with a low annual probability of malignant transformation, such as IgM-MGUS, can actually confer a survival advantage through the clinical benefits of monitoring programs started after such a diagnosis. As long as an IgM-MGUS does not evolve, the medical surveillance it promotes is probably more accurate and frequent than that which members of the general population undergo in the absence of a specific health problem. Stricter medical control (at least every 6 months in our series), applied to mature or elderly patients, can identify and correct many coexisting or silent pathologic conditions, acting as a more efficient preventive care program. In this way, the reduced mortality in patients with IgM-MGUS might be attributed to early identification and correction of risk factors for cardiovascular disease (hypertension, diabetes, hyperlipoproteinemia, and obesity) and to early diagnosis and treatment of second cancers and acute or chronic common infectious diseases and their complications, which can be hypothesized to occur in carriers of an IgM gammopathy. Unfortunately, this hypothesis cannot be verified from our available data (although it can be advocated to partially counterbalance a probably higher disease-related mortality of the patients with A-WM, resulting in a nearly normal overall survival). Other reasons for a survival advantage (possibly related to functional properties of the lymphocyte clone or to activity of monoclonal IgM in the serum) cannot be excluded, but seem less likely. In a series of 213 patients with IgM-MGUS, Kyle et al. (3) observed a significantly lower survival than that which would have been expected among Minnesota residents. However, their population of patients had a higher median age at diagnosis (74 versus 65 years) and higher median serum monoclonal protein (12.0 versus 8.8 g/L).

Finally, it is interesting to note that of the various clinical entities identifiable among IgM gammopathies (excluding IgM-related disorders, which escaped the present study), only S-WM showed a mortality rate clearly higher than that of the general population. In the comparison with IgM-MGUS and A-WM, besides some differences in epidemiologic and clinical characteristics (IgM concentration or percent of marrow infiltration), which paralleled the observed variations in SMR, the only substantial difference that might explain the prognostic differences is symptomaticity itself. This, as a whole, is by definition a necessary and sufficient requirement for the discrimination between A-WM and S-WM and is also absent by definition in patients with IgM-MGUS. The distinction of a more favorable clinical form of WM, characterized by the absence of symptoms or, specifically, of a given symptom (8), is well known and in the last decade was defined as “smoldering” (9, 10) or “asymptomatic” WM (11). Because it is well recognized that

Table 2 Variations of SMR recorded after dividing the patients with A-WM and S-WM into subgroups according to their percentages of bone marrow lymphocytes or serum IgM concentrations at presentation being above or below the median cutoff limit

<table>
<thead>
<tr>
<th>Marrow infiltration (%)</th>
<th>No. of patients</th>
<th>SMR</th>
<th>Serum IgM concentration (g/L)</th>
<th>No. of patients</th>
<th>SMR</th>
</tr>
</thead>
<tbody>
<tr>
<td>A-WM</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≥20</td>
<td>118</td>
<td>1.668</td>
<td>&gt;15</td>
<td>99</td>
<td>1.574</td>
</tr>
<tr>
<td>&lt;20</td>
<td>99</td>
<td>1.136</td>
<td>≤15</td>
<td>118</td>
<td>1.207</td>
</tr>
<tr>
<td>S-WM</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≥50</td>
<td>133</td>
<td>6.190</td>
<td>&gt;25</td>
<td>124</td>
<td>5.228</td>
</tr>
<tr>
<td>&lt;50</td>
<td>141</td>
<td>4.803</td>
<td>≤25</td>
<td>150</td>
<td>5.620</td>
</tr>
</tbody>
</table>

NOTE. None of the differences in SMR values was statistically significant.
constitutional symptoms are due to a number of cytokines (12, 13), many of which can act as an autocrine stimulus to cell proliferation, it is very likely that the appearance of general symptoms during the course of an IgM gammopathy corresponds to a new step in the neoplastic sequence (or to a new functional ability) of the cell clone, which may favor either proliferation activity or dysregulation of apoptosis (14, 15). In other terms, the appearance of symptoms might mark a switch toward a more aggressive clinical behavior.

In conclusion, the recently proposed international diagnostic criteria can be considered to have been substantially validated by our findings for three of the four clinicopathologic entities defined. Moreover, it can be added that the crucial diagnostic parameter, which also acts as a powerful prognostic determinant, is the onset of symptoms related to the biological activity of either the tumor cell clone or the monoclonal protein, whereas the mere levels of serum IgM or bone marrow infiltration have little importance.

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Prognostic Validation of the International Classification of Immunoglobulin M Gammopathies: A Survival Advantage for Patients with Immunoglobulin M Monoclonal Gammopathy of Undetermined Significance?

Paolo G. Gobbi, Luca Baldini, Chiara Broglia, et al.


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