Role of Different Hematologic Variables in Defining the Risk of Malignant Transformation in Monoclonal Gammopathy

By L. Baldini, A. Guffanti, B.M. Cesana, M. Colombi, O. Chiorboli, I. Damilano, and A.T. Maiolo

The presenting clinico-hematologic features of 386 patients with nonmyelomatous monoclonal gammopathy (MG) were correlated with the frequency of malignant transformation to evaluate the most important variables conditioning its evolution into multiple myeloma (MM) or Waldenström macroglobulinemia (WM). Most of the patients (335) had monoclonal gammopathy of undetermined significance (MGUS: 39 IgA, 242 IgG, 54 IgM); the remaining 51 patients (12 IgA, 39 IgG) fulfilled all of the MGUS diagnostic criteria (according to Durie) except that bone marrow plasma cell (BMPC) content was 10% to 30%, and so they were defined as having monoclonal gammopathy of borderline significance (MGBS). There were no significant differences between the MGUS and MGBS groups in terms of age, sex, or median follow-up. After a median follow-up of 70 and 53 months, respectively, 23 of 335 MGUS and 19 of 51 MGBS patients had undergone a malignant evolution. Univariate analysis of the IgA and IgG patients showed that the cumulative probability of the disease evolving into MM correlated with diagnostic definition (MGBS vs MGUS), BMPC content (≥10% vs <5% and ≤5% vs >5%) and reduced serum polyclonal Ig. In the IgG cases, there was also a significant correlation with detectable Bence Jones proteinuria, serum monoclonal component (MC) levels and age at diagnosis (>70 vs ≤55 years). In the IgG cases as a whole, the same variables remained in the Cox model where the BMPC percentage was considered after natural logarithmic transformation and the monoclonal component as g/dL value. The relative risks of developing MM are the following: 2.4 for each 1 g/dL increase of IgG serum MC, 3.5 for detectable light chain proteinuria, 4.4 for the increase of 1 unit in log, BMPC percentage, 6.1 for age >70, 3.6 and 13.1 for a reduction in one or two polyclonal Ig. In conclusion, our study allows the identification of a particular subset of MGUS patients (MC ≤1.5 g/dL, BMPC <5%, no reduction in polyclonal Ig and no detectable light chain proteinuria) at very low-risk of evolution, who can be considered as having benign monoclonal gammopathies. We also describe a previously undefined group of MG patients (with monoclonal gammopathy of borderline significance) who are at high-risk of malignant evolution. These findings could have a considerable impact on the cost/benefit ratio of monitoring programs in these patients.

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and without any symptoms, associated disease features, or recurrent infections. SMM was defined as an indolent MM, but without any demonstrable bone lesion and with BMPC levels of 10% to 30%. SMM differed from MGBS in terms of the upper limit of serum and urine MC concentrations and the number of reduced polyclonal immunoglobulin (Ig) classes (could be double in SMM). The lower reference limits of serum Ig levels were calculated on the basis of the mean value minus 2 standard deviations (SD) of a series of serum Ig level evaluations in healthy subjects (IgA: 70 mg/dL; IgG: 600 mg/dL; IgM: 50 mg/dL); except for IgA, these are identical to those reported by Durie.4

The IgM MGUS group was defined on the basis of the following: MC < 3 g/dL, Bence Jones proteinuria < 1 g/24 hours, lymphocytic or lymphoplasmocytic bone marrow infiltrate < 30%, a normal or nodular bone marrow histologic pattern, no symptoms, and normal cell counts.8 The Waldenström’s macroglobulinemia (WM) group was defined as follows: anemia (Hb < 11 g/dL) in the presence of a serum IgM MC (frequently but not always > 3 g/dL), lymphocytic/lymphoplasmocytic bone marrow infiltrate > 30% with a diffuse bone marrow histologic pattern, variably associated with thrombocytopenia (platelets < 100,000 per μL), peripheral monoclonal lymphocytosis (evaluated as light chain surface Ig restriction in those patients with lymphocytosis > 4,000 per μL), asymptomatic splenomegaly. The patients who fell into either of these last two groups were classified as having indolent WM.9

Laboratory and clinical studies. Beside the usual laboratory tests (with serum calcium, liver, and kidney functions), we defined the type of M-protein by means of immunofixation and quantified it using serum protein electrophoresis. Serum polyclonal immunoglobulins were measured by means of nephelometry, and light chain proteinuria by means of cellulose acetate electrophoresis on 100-fold concentrated urine. Under our conditions, the lowest detectable level of Bence Jones proteinuria was 100 mg/L. The usual laboratory tests and the serum and urinary MC evaluations were performed three times a year for the first 2 years and then every 6 months. Bone marrow aspirates and skeletal x-rays were obtained at diagnosis and every time they were considered necessary during follow-up. In the MGBS patients, bone marrow aspiration was performed every year and skeletal x-rays every 2 to 3 years. The BMPC percentages were the mean value of two 400-cell counts separately made by two experienced hematologists. In the MGBS group, the count was repeated every year and, in all of the cases included in the study, it was always > 10%.

Statistical methods. Descriptive statistics were calculated for quantitative (mean, SD, minimum, maximum, and median in the case of asymmetric distribution) and qualitative variables (absolute and relative frequencies). Comparisons between the diagnostic classes were made by means of the nonparametric analysis of variance for quantitative variables, and the chi-square test for qualitative variables. Multiple aposteriori comparisons between each pair of the same qualitative variable were performed following the Bonferroni approach. For the analysis of the time to evolution, the follow-up was truncated at 7 years to obtain reliable estimates of the cumulative actuarial probability of no evolution calculated according to the method of Berkson and Gage.7 Comparisons between strata were made using the log rank test.8 The best subset of prognostic factors was obtained following Cox’s multivariate model according to a backward procedure, its assumptions being checked by means of the graphical method.10 This model was only applied to the IgG cases because of the small number of patients in the IgA group. The BMPC percentages have been natural logarithm transformed because of their positively skewed distribution; then the natural logarithm of BMPC percentage and the serum level of M-component have been considered as continuous variables. In the univariate and multivariate analyses, the time to evolution was calculated starting 12 months after the first clinical/laboratory evaluation.

RESULTS

On the basis of the adopted diagnostic criteria for MGUS and MGBS, the patients were divided as shown in Table 1. Serum MC levels were significantly different between the MGUS and MGBS groups (P = .034 for IgA cases and P < .001 for IgG cases). The total number of patients with a reduction in serum polyclonal Ig was significantly higher in the MGBS (45.1%) than the IgA/IgG MGUS group (23.1%; P = .002). A reduction in polyclonal Ig was less frequent in the IgM MGUS than in the other MGUS patients (3.7% vs 28.2% for IgA and 22.3% for IgG; P = .003). All-patient analysis of the frequency of a reduction in polyclonal Ig by Ig class showed that IgG was less frequently involved (P = .015): in particular, a reduction in polyclonal IgA was present in 11.4% of the patients with MGUS versus 23% of those with MGBS, IgG in 4.3% versus 8.3%, and IgM in 14.2% versus 25.5%. As shown in Table 1, the duration of follow-up was not significantly different between the two diagnostic groups. Table 2 shows the absolute number of patients developing MM or WM, the median follow-up time to evolution and the minimum and maximum values. The frequency of malignant transformation in the MGUS and MGBS groups was respectively 6.8% (median follow-up, 70 months) and 37% (median follow-up, 53 months). The frequency of malignant transformation in patients with IgM MGUS was not substantially different from that in patients with IgA and IgG MGUS (7.4% vs 10.2% and 6.2%, respectively). The frequency of patients experiencing a malignant transformation was similar for the first 5 years of follow-up (5, 7, 4, 4, and 5 patients per year); the remaining two evolutions occurred in the sixth and seventh year of follow-up. Five of the 19 cases of MM that evolved from IgA/IgG MGUS and of 14 cases that evolved from IgA/IgG MGBS had the clinico-hematologic features of indolent MM; all of these patients showed limited bone involvement and none required treatment at a median follow-up of 10 months (4 to 15 months). One of the four cases of WM that evolved from IgM MGUS showed an indolent clinical course (serum MC = 5.8 g/dL, Hb = 11.1 g/dL, diffuse bone marrow infiltration and splenomegaly) and did not receive any treatment for 9 months after evolution. Table 3 shows the 95% confidence intervals of the cumulative probability of no evolution to MM at 60 months, and the P value of the log rank test. Regarding serum MC and BMPC percentages, the results from cases obtained by means of different cut-offs are shown mainly for illustrative purposes to determine if their clinical relevance was consistent with a statistical significance as a criterion for their prognostic meaning. Figure 1 shows that the probability of no evolution was significantly higher for MGUS than for MGBS (P < .001); this can also be seen in the significantly reduced cumulative probability of no malignant transformation in patients with more than 10% BMPC (P < .001 and P = .027 for the IgG and IgA forms, respectively; Fig 2). In both IgA and IgG cases, the reduction in one or two serum polyclonal Ig was associated with a reduced cumulative probability of no evolution (P < .001 and P = .009, respectively). In IgG patients, this was also the case in the presence of detectable Bence Jones proteinuria (P < .001), and serum MC levels > 1.9 or > 1.5 g/dL (P < .001 and P = .003) (Fig 2). On the contrary,
Table 1. Characteristics of MGUS and MGBS Patients

<table>
<thead>
<tr>
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<th>MGUS</th>
<th>MGBS</th>
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<tbody>
<tr>
<td>No. of patients</td>
<td>39</td>
<td>242</td>
</tr>
<tr>
<td>Age (yr, mean ± SD)</td>
<td>58.3 ± 12.0</td>
<td>57.8 ± 12.9</td>
</tr>
<tr>
<td>M/F ratio</td>
<td>0.95</td>
<td>1.12</td>
</tr>
<tr>
<td>κ/λ ratio</td>
<td>0.95</td>
<td>1.87</td>
</tr>
<tr>
<td>Serum MC (g/dL; mean ± SD)</td>
<td>1.16 ± 0.4*</td>
<td>1.55 ± 0.51t</td>
</tr>
<tr>
<td></td>
<td>3.89</td>
<td>3.49</td>
</tr>
<tr>
<td>Malignant proteinuria</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Bone-marrow plasma cells %</td>
<td>2.50 ± 2.46</td>
<td>3.99 ± 2.52</td>
</tr>
<tr>
<td>Follow-up (mo; median, min-max)</td>
<td>107</td>
<td>65 (13-169)</td>
</tr>
</tbody>
</table>

* P = .034.
† P < .001.
‡ P = .002.
§ Lymphoplasmocytes and plasma cells.

no relationship was found with the MC heavy-chain class, light chain type, or sex. In the IgG group, the patients who were more than 70 years old at the time of diagnosis fared worse (at a borderline level of significance) than those aged 55 years or less. At multivariate analysis the subset of variables that significantly correlated with evolution to MM in IgG cases included the degree of BMPC infiltration (P < .001), reduction in polyclonal Ig (P = .003), age at diagnosis (P = .016), Bence Jones proteinuria (P = .009), and serum MC level (P = .020). For each variable, the relative risk (RR) of developing MM (with its 95% confidence intervals) is shown in Table 4. The prognostic index was calculated for each patient according to the formula shown at the bottom of Table 4. Dividing the distribution of the prognostic index into quartiles, we obtain one event under the median (65.0), five events in the third quartile (from 65.1 to 82.0), and 21 events in the last quartile. In addition, the risk of transformation is 3.9 until a prognostic index of 600, 29.0 for a prognostic index ranging from 601 to 2,500 and 46.4 for the higher values. In all of the IgG cases, comparison of the mean MC levels of stable versus evolved forms, at diagnosis, and after 1 and 2 years of follow-up, shows significantly higher values in the evolved forms (P < .005).

Finally, we can identify the existence of a group of MG patients characterized by a low-rate of progression to MM. We suggest that low-risk MGUS should be defined as follows: no reduction in polyclonal Ig, undetectable light chain proteinuria, BMPC <5% and low MC concentrations (IgG ≤1.5 g/dL). Of the 77 IgG MG patients with these characteristics, only one evolved and then only to indolent MM (the median follow-up of this group was 66.9 months; minimum 12.0, maximum 205.3). Our analysis is not capable of suggesting a safe MC level for IgA, however of the 15 IgA MG cases with these characteristics, none progressed (median follow-up 64.8 months; minimum 18.8, maximum 158.6).

DISCUSSION

Monoclonal gammopathies arise from lympho/plasmacytic clonal expansions, which may be limited and regulated or, as in MM or Waldenström macroglobulinemia, uncontrolled. The controlled forms, such as MGUS and SMM, are stable by definition and so a conservative approach of...
For the diagnostic definition of MGUS, SMM, and MM in our study, we used the criteria suggested by Durie.7 Some of our IgA and IgG cases (51 patients) could not be classified as MGUS or SMM because of their BMPC percentage and serum MC levels and were, therefore, defined as MGBS (see Materials and Methods). The aims of this study were the following: (1) to evaluate the frequency of malignant transformation in the different types of MGUS and compare it with that of MGBS; (2) to detect the frequency with which MGBS evolves into symptomatic MM to understand whether it should be considered a MGUS or rather an indolent form of MM; and (3) in IgA and IgG cases, to analyze the value of some simple hematologic variables in defining situations with different probabilities of malignant transformation.

In our MGUS group the frequency of progression (6.8% after a median follow-up of 70 months) was a little lower than that recently reported by Blade13 (10.2% after a median follow-up of 56 months); the data is not easily comparable with that of Kyle12 because of the different duration of follow-up (24% after a median follow-up of 264 months). In terms of cumulative probability of no evolution at 60 months, our data (95% CI, 0.910 to 0.971) agree with the figures reported by these investigators.

The propensity to evolve into MM was higher in MGBS.
The predictive significance of the percentage of BMPC is a matter of debate. Some investigators believe that the upper limit of safety in MGUS should be 5%, although they recognize that some patients with a greater degree of plasmacytosis may remain in a stable condition for prolonged periods. Others have suggested that the upper limit can normally be fixed at 10%, possibly excluding aggregates on biopsy. On the other hand, in a recent analysis of 684 MG patients, Ucci et al. found that 20% of BMPC could be taken as a safe cut-off point for the differentiation of MGUS from early MM, an observation which is in line with the data reported by Blade et al.; although it must be stressed...
that the median follow-up of Ucci’s study was relatively short and that Blade’s population was limited. Our analysis confirmed the importance of 10% BMPC as the upper limit for a diagnosis of MGUS, as higher percentages frequently identified situations with a worse clinical outcome. The prognostic importance of the percentage of BMPC is further underlined by the finding of a low-rate of evolution in patients with a BMPC percentage <5%.

When considering the relevance of serum MC class to the evolution of MGUS and MGBS, we did not find any significant difference between IgA and IgG MG. This finding also emerges from the larger population studied by Kyle, although it is in disagreement with Blade et al, who found that a different heavy chain immunoglobulin class (α v γ) was predictive of an increased probability of malignant transformation. Furthermore, we did not observe any significant differences in the malignant evolution of IgM, IgA and IgG MGUS.

Much has been said concerning the prognostic importance of serum MC levels. Durie has suggested different discriminatory levels for serum IgG and IgA MC (<3.5 g/dL and <2.0 g/dL, respectively), but Greipp has proposed a generic MC concentration of <3 g/dL, regardless of the Ig class. Ucci et al indicated that a serum MC concentration of 1.6 versus 2.2 significantly helped in the differentiation of MGUS from indolent MM. Moller-Petersen et al observed an association between higher serum MC levels and a greater likelihood of malignancy, but other investigators have not reached the same general conclusions. In our IgA/IgG MG cases, univariate analysis showed a significant propensity towards progression to MM only in the larger group of IgG cases, with a higher probability in patients whose level of serum MC was >1.9 and >1.5 versus ≤1.3 and ≤1.5 g/dL, respectively. Moreover, serum MC levels as each 1 g/dL increase maintained their prognostic value at multivariate analysis. Analysis of mean serum MC concentrations at diagnosis, and after 1 and 2 years of follow-up, showed significantly higher values in those patients whose IgG MG evolved into MM. The fact that this difference is evident from the time of diagnosis does not eliminate the importance of the trend in MC levels as one of the indicators of disease progression.

Reduced levels of uninvolved Ig may be observed in MGUS. Peltonen noted a reduction in one or two polyclonal Ig in 38% and 44%, respectively, of MGUS patients; unfortunately these were not prospective studies and so we don’t know how patients with Ig reduction would have fared in comparison with those without this feature. Ucci et al observed that a reduction in normal Ig was preferentially associated with a diagnosis of MM. In the Mayo Clinic prospective study, there was no significant difference in the levels of normal Ig between the stable and the progressive forms of MGUS. In our study, a reduction in polyclonal Ig correlated well with a higher frequency of progression to MM at both univariate and multivariate analysis. These data suggest that the impact of neoplastic clones on normal antibody production can be considered a predictive marker of malignancy.

The presence of Bence Jones proteinuria is not considered a sure index of pathological clone instability. In this regard some investigators have suggested that even high risk correlated with a small amount of Bence Jones proteinuria, while others did not confirm this association. In his commonly applied criteria for MGUS, Durie considered only Bence Jones proteinuria levels of >1 gr/24 hours as surely malignant (in the presence of other criteria of benignity). In our IgA/IgG MG cases, detectable light chain proteinuria was another feature significantly associated with a higher rate of malignant transformation. In particular, the prognostic significance of this variable in IgG cases was also confirmed at multivariate analysis. As in Kyle’s study, we did not find that differences in sex or albumin levels (data not shown) affected the probability of evolution. On the other hand, we did find that an age at diagnosis of more than 70 years was associated with a worse prognosis, and this was confirmed at multivariate analysis. Beta-2 microglobulin and the plasma cell labeling index, which were evaluated only in some of the patients in our population, do not seem to be useful in defining the stability of MGUS. Their importance lies in the fact that they can aid the diagnosis of present or imminent symptomatic MM versus indolent MM and MGUS.

The main goal of prospective studies such as ours is to identify situations with a particularly low probability of malignant transformation on the basis of simple hematologic parameters. Given the increasing frequency of newly-diagnosed cases, this could lead to an appreciable advantage in terms of patients’ psychological involvement and also reduce the frequency and cost of medical interventions at diagnosis and during follow-up. Taking into account the observations made by other investigators, our results seem to indicate the existence of a group of MG characterized by a low rate of progression to MM. In a preliminary way, we suggest that low-risk IgA and IgG MGUS should be defined as follows: no reduction in polyclonal Ig, undetectable light chain proteinuria, BMPC <5% and low MC concentrations (IgG ≤1.5 g/dL). In patients with these characteristics, skeletal x-rays and narrow examinations need not be done until there is evidence of progressive disease, moreover they can enter a less intensive follow-up with blood and urine tests repeated every 4 months for the first year and then every 6 months. In situations with less favorable characteristics, more in-depth investigations should be performed and a closer follow-up instituted.

In conclusion, this study provides some suggestions for recognizing certain features capable of predicting which of these clonal disorders will remain stable and which may undergo malignant transformation. Secondly, on the basis of these features, we identify a particular subset of MGUS forms with a quite low propensity to evolution and that can be considered as a benign group of monoclonal gammopathies. Finally we describe a group of previously unidentified patients with what we have called “monoclonal gammopathy of borderline significance,” who are at high risk of malignant evolution.

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