Serum free light chain ratio is an independent risk factor for progression in monoclonal gammopathy of undetermined significance


We hypothesized that the presence of monoclonal free kappa or lambda immunoglobulin light chains in monoclonal gammopathy of undetermined significance (MGUS), as detected by the serum free light chain (FLC) assay increases the risk of progression to malignancy. Of 1384 patients with MGUS from Southeastern Minnesota seen at the Mayo Clinic from 1960 to 1994, baseline serum samples obtained within 30 days of diagnosis were available in 1148. At a median follow-up of 15 years, malignant progression had occurred in 87 (7.6%) patients. An abnormal FLC ratio (kappa-lambda ratio < 0.26 or > 1.65) was detected in 379 (33%) patients. The risk of progression in patients with an abnormal FLC ratio was significantly higher compared with patients with a normal ratio (hazard ratio, 3.5; 95% confidence interval [CI], 2.3-5.5; \( P < .001 \)) and was independent of the size and type of the serum monoclonal (M) protein. Patients with an abnormal serum FLC ratio, non-immunoglobulin G (non-IgG) MGUS, and a high serum M protein level (\( \geq 15 \) g/L) had a risk of progression at 20 years of 58% (high-risk MGUS) versus 37% with any 2 of these risk factors (high-intermediate risk), 21% with one risk factor (low-intermediate risk), and 5% when none of the risk factors were present (low risk). (Blood. 2005; 106:812-817)

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The assay is performed on automated chemistry analyzers, is widely available, and is commonly used to monitor patients with oligo-secretory or nonsecretory myeloma and primary amyloidosis, as well as patients with the light-chain only form of myeloma. The presence of a monoclonal FLC in MGUS may be a marker of clonal evolution in the neoplastic plasma cell since it likely indicates a loss of control over the proportion of heavy and light chains synthesized. We undertook this study to test the hypothesis that an abnormal FLC ratio at baseline is a risk factor for the progression of MGUS to malignancy.

Materials and methods

The study cohort was derived from persons who resided in the 11 counties in southeastern Minnesota who met previously established diagnostic criteria for MGUS at the Mayo Clinic from January 1, 1960, through December 31, 1994. Of 1384 patients with MGUS diagnosed during this period, a cohort whose baseline characteristics, methods of detection, follow-up, and risk of progression have been well described by us earlier, 1148 patients who had cryopreserved serum samples collected within 30 days of the MGUS diagnosis were studied. Follow-up was through the review of each patient’s complete medical records at the Mayo Clinic. The study was approved by the Mayo Institutional Review Board.

The FLC level in serum collected at the time MGUS was first recognized was determined on all 1148 patient samples using the FLC assay (Freelite; The Binding Site, Birmingham, United Kingdom) performed on a Dade-Behring Nephelometer (Deerfield, IL). It consists of 2 separate measurements, one to detect free-kappa (normal range, 3.3-19.4 mg/L) and the other to detect free-lambda (normal range, 5.7-26.3 mg/L) light chains. In addition to measuring the absolute levels of FLC, the test also allows the assessment of clonality based on the ratio of kappa-lambda light chain.
chain levels (normal range, 0.26-1.65).13 Patients with a kappa-lambda FLC ratio less than 0.26 are typically defined as having monoclonal lambda FLC and those with ratios greater than 1.65 are defined as having a monoclonal kappa FLC. If the FLC ratio is greater than 1.65, kappa is considered to be the “involved” FLC and lambda the “uninvolved” FLC, and vice versa if the ratio is less than 0.26.

The normal reference range of 0.26 to 1.65 for the free-kappa–lambda ratio in the FLC assay reflects a higher serum level of free-lambda light chains than would be expected given the usual kappa-lambda ratio of 2 for intact immunoglobulins. This occurs because the renal excretion of free kappa (which exists usually in a monomeric state) is much faster than free lambda (which is usually in a dimeric state).13,14

FLCs

The prognostic effect of abnormal kappa-to-lambda FLC ratio on progression of MGUS was studied. We also examined whether the risk of progression varied depending on the extent to which the FLC ratio was abnormal. To estimate the continuous risk effect of the FLC ratio, a smoothing spline as previously described17 was used in univariate and multivariate Cox proportional hazards models.18 The risk of progression depending on extent to which the FLC ratio was abnormal was also estimated after adjusting for the size of the serum monoclonal protein to the mean monoclonal protein level. The primary end point was progression to multiple myeloma or a related disorder. Progression endpoints were examined both as cumulative probability of progression and cumulative incidence. The former was computed using an ordinary Kaplan-Meier estimate19 where patients who die are censored; curves were compared using the log-rank test. The effects of potential risk factors on progression rates were examined using a Cox proportional hazards model.18 The cumulative incidence curve, on the other hand, explicitly accounts for death from other causes (such as cardiovascular disease, cerebrovascular disease, or unrelated malignancy) as a competing risk and was estimated using the method of Gooley.20

Results

Clinical characteristics

The median age at diagnosis of MGUS was 72 years. The median serum M protein at diagnosis was 12 g/L. Urine electrophoresis and immunoelctrophoresis or immunofixation was done in 370 patients. Of these, a monoclonal light chain was detected in 110 patients (30%). Additional patient characteristics are given in Table 1.

Serum FLC assay

The free-kappa light chain values ranged from 0.1 mg/L to 1210 mg/L (median, 20 mg/L), whereas the free-lambda light chain values ranged from 0.1 mg/L to 10 100 mg/L (median, 20 mg/L). There were 737 patients (64%) who had elevated levels of kappa or lambda FLC. The kappa-to-lambda ratio ranged from 0.002 to 94.2 (median, 1.0). Based on the normal reference range for kappa-lambda ratio currently in use for clinical practice (0.26-1.65),13 an abnormal FLC ratio (indicating the presence of monoclonal FLCs) was detected in 379 (33%) patients. Of these, the FLC was of the same isotype (kappa or lambda) as the corresponding serum M protein in 371 (98%) of the patients. A higher proportion of patients with a positive urinary monoclonal protein had an abnormal FLC ratio (55%) compared with patients with no detectable monoclonal proteins in the urine (32%) (P < .001).

Outcomes

These 1148 patients were followed for a total of 8982 person years (median, 15 years). There were 783 patients (68%) who were followed until death. During this period of observation, 87 (7.6%) patients experienced progression: multiple myeloma (53 patients), IgM lymphoma (17 patients), primary amyloidosis (6 patients), macroglubulinemia (6 patients), chronic lymphocytic leukemia (3 patients), and plasmacytoma (2 patients). The cumulative probability of progression was 9% at 10 years, 20% at 20 years, and 30% at 25 years, or approximately 1% per year (Figure 1). Because patients who die are censored, the upper curve in this figure reflects the probability that a patient who has not died of other causes will experience plasma cell progression at each point in the follow-up; it therefore represents the natural history of the disease assuming patients do not die of other causes prior to progression. The risk of progression is lower if competing causes of death are taken into account, 11.2% at 25 years, as illustrated by the lower curve in Figure 1A.

Risk of progression based on FLC assay

In a Cox proportional hazards model, the risk of progression in patients with an abnormal FLC ratio was significantly higher compared with patients with a normal ratio (hazard ratio, 3.5; 95%
Multivariate analysis and proposed model for predicting risk of progression of MGUS

The effect of an abnormal FLC ratio on risk of progression was independent of the size of the M protein, as illustrated in Figure 2B, which has been adjusted for the size of the serum M protein. After adjusting for the size and type of the serum M protein on multivariate analysis, the hazard ratio for progression associated with an abnormal FLC ratio was only slightly reduced (hazard ratio, 2.6; 95% CI, 1.7-4.2; P < .001) as delineated in Table 3. In this multivariate model the hazard ratio for the size of the serum M protein was 2.4 (P < .001) and that for a non-IgG type MGUS was 2.6 (P < .001).

Risk stratification model for MGUS

The FLC ratio added additional prognostic value to all 3 subgroups of MGUS stratified by the 2 known prognostic factors, the size and type of M protein (Table 4). We constructed a model for predicting the risk of progression of MGUS based on the size of the serum M protein, the type of immunoglobulin, and the presence of an abnormal FLC ratio (< 0.26 or > 1.65). The use of these 3 risk factors identified 4 cohorts of patients with MGUS with significantly different rates of progression (Table 4; Figure 3). In fact, when competing causes of death are taken into account, the true lifetime risk of progression decreases to 2% for patients in the low-risk group.

Discussion

The term “MGUS” was first coined at the Mayo Clinic more than 25 years ago, and our studies have shown that the risk of progression of MGUS to myeloma or related malignancy is approximately 1% per year. However, distinguishing the patient with a stable monoclonal gammopathy from one in whom multiple myeloma or related disorders will eventually develop is difficult when MGUS is originally recognized. Moreover, there is no decline in the risk of progression over time, necessitating lifelong follow-up, usually performed by primary-care providers. Patients are referred to hematologists typically in the face of a rising M

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**Table 3. Multivariate analysis of prognostic factors for progression of monoclonal gammopathy of undetermined significance**

<table>
<thead>
<tr>
<th>Prognostic factor</th>
<th>Hazard ratio (95% confidence interval)*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Abnormal FLC ratio</td>
<td>2.6 (1.7-4.2)</td>
</tr>
<tr>
<td>Serum M protein size</td>
<td>2.4 (1.7-3.5)</td>
</tr>
<tr>
<td>IgA, IgM, or biclonal IgA plus IgM</td>
<td>2.6 (1.7-4.0)</td>
</tr>
</tbody>
</table>

*P < .001 for each variable.

**Table 4. Risk-stratification models to predict progression of monoclonal gammopathy of undetermined significance to myeloma or related disorders**

<table>
<thead>
<tr>
<th>Risk group</th>
<th>No. patients</th>
<th>Relative risk, 95% CI</th>
<th>Absolute risk of progression at 20 years, %</th>
<th>Absolute risk of progression at 20 years accounting for death as a competing risk, %</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Addition of FLC ratio to known prognostic categories</strong></td>
<td></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Low risk (serum M protein &lt; 15 g/L and IgG subtype)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Normal FLC ratio</td>
<td>449</td>
<td>1</td>
<td>5</td>
<td>2</td>
</tr>
<tr>
<td>Abnormal FLC ratio</td>
<td>142</td>
<td>7.4</td>
<td>27</td>
<td>12</td>
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<tr>
<td>Intermediate risk (either serum M protein ≥ 15 g/L or non-IgG subtype)</td>
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<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Normal FLC ratio</td>
<td>278</td>
<td>1</td>
<td>22</td>
<td>9</td>
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<tr>
<td>Abnormal FLC ratio</td>
<td>184</td>
<td>2.2</td>
<td>37</td>
<td>17</td>
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<tr>
<td>High risk (serum M protein ≥ 15 g/L and non-IgG subtype)</td>
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<td></td>
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<tr>
<td>Normal FLC ratio</td>
<td>42</td>
<td>1</td>
<td>37</td>
<td>23</td>
</tr>
<tr>
<td>Abnormal FLC ratio</td>
<td>53</td>
<td>1.5</td>
<td>58</td>
<td>27</td>
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<tr>
<td><strong>Risk stratification model incorporating all 3 predictive factors</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Low risk (serum M protein &lt; 15 g/dL, IgG subtype, normal FLC ratio [0.26-1.65])</td>
<td>449</td>
<td>1</td>
<td>5</td>
<td>2</td>
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<tr>
<td>Low-intermediate risk (any 1 factor abnormal)</td>
<td>420</td>
<td>5.4</td>
<td>21</td>
<td>10</td>
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<tr>
<td>High-intermediate risk (any 2 factors abnormal)</td>
<td>226</td>
<td>10.1</td>
<td>37</td>
<td>18</td>
</tr>
<tr>
<td>High risk (all 3 factors abnormal)</td>
<td>53</td>
<td>20.8</td>
<td>58</td>
<td>27</td>
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</table>
established population-based cohort of patients with MGUS in order to validating and confirming these findings in a large, well-defined population-based cohort of patients with MGUS who had progression to myeloma or related disorder who served as cases, while 50 patients with MGUS who had progression to myeloma or related disorder identified in this study will serve as the base from which additional risk factors can identify a suitable cohort for chemoprevention trials.

Recent studies show that loss of heavy chain expression in myeloma is related to cytogenetic events in the heavy chain locus on chromosome 14 (14q32). We hypothesize that clonal evolution of the neoplastic plasma cell may be marked by imbalance in heavy and light chain production, and the results of this study lend support to this theory. Whether the expression of excess clonal FLCs in MGUS evolves from a cell that has undergone additional cytogenetic changes, or represents a clone that has aberrant light chain overexpression from the outset, needs further investigation.

The serum FLC assay used in this study is currently used clinically to monitor response to therapy in patients with myeloma who present with unmeasurable levels of monoclonal protein in serum and urine protein electrophoresis studies (oligo-secretory or nonsecretory disease). In these patients, the serum FLC levels are often elevated, decreasing the need for serial bone marrow biopsies. It is also used in a similar manner in patients with primary amyloidosis who often have low or unmeasurable levels of monoclonal protein by electrophoresis. The FLC assay is also being investigated as a replacement to 24-hour urine electrophoresis studies to monitor light chain excretion in the urine.

The presence of an abnormal FLC ratio is a clinically and statistically significant predictor of progression in MGUS. We identify a low-risk subset of patients with MGUS with a remarkably small lifetime risk of progression in whom less frequent follow-up can be justified. Since this subset accounts for almost 40% of all patients, this is a finding of significant importance for the management of MGUS.

References


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