Incidence, clinical course, and prognosis of secondary monoclonal gammopathy of undetermined significance in patients with multiple myeloma

Rishi K. Wadhera, MD
Robert A. Kyle, MD
Dirk R. Larson, MS
Angela Dispenzieri, MD
Shaji Kumar, MD
Hillard M. Lazarus, MD
S. Vincent Rajkumar, MD

From the Department of Medicine, Mayo Medical School, Rochester, MN, the Division of Hematology, Mayo Clinic, Rochester, MN, the Department of Biostatistics, Mayo Clinic, Rochester, MN, and the University Hospitals Case Medical Center and the Ireland Cancer Center and Case Comprehensive Cancer Center, Cleveland, OH, USA

Correspondence to; S. Vincent Rajkumar, MD, Division of Hematology, Mayo Clinic, Rochester, MN 55905; Phone 507-538-0591; Fax: 507-266-4972;
Email: rajkumar.vincent@mayo.edu
Abstract

During the course of multiple myeloma (MM), new monoclonal (M) proteins of an isotype distinct from the original clone referred to as secondary monoclonal gammopathy of undetermined significance (MGUS) have been described. We report on the frequency, characteristics, and outcome of secondary MGUS. Of the 1,942 patients with MM, 128 (6.6%) developed a secondary MGUS, at a median time of 12 months from the diagnosis of MM. The median duration of secondary MGUS was 5.9 months. Secondary MGUS was more common in patients following stem cell transplantation compared with those who had not undergone such treatment (22.7% versus 1.6%), P<0.001. Overall survival (OS) was significantly superior in MM patients who developed secondary MGUS compared with the rest of the cohort, 73 months versus 38 months respectively, P<0.001. The time of onset and duration of secondary MGUS, and failure to resolve spontaneously had an effect on OS and needs further study.
Monoclonal Gammopathy of Undetermined Significance (MGUS) is a premalignant plasma cell disorder\textsuperscript{1-3}. It is present in 3-4\% of the general population over the age of 50\textsuperscript{4}. The prevalence of MGUS increases with age\textsuperscript{5-9} and toxin exposure\textsuperscript{10}. MGUS progresses to multiple myeloma (MM) or related malignancy at a rate of 1\% per year\textsuperscript{3,11,12}. At 25 years of follow up, the probability of progression is 11\% adjusting for competing causes of mortality\textsuperscript{13-15}. Osteoporosis, neuropathy, and thrombophlebitis have been associated with MGUS\textsuperscript{16}.

Previous studies have found that during the course of MM, new monoclonal gammopathies of an isotype (heavy and/or light chain) distinct from the original MM can emerge\textsuperscript{17, 18}. This entity, termed secondary MGUS\textsuperscript{17}, has been hypothesized to be due to recapitulation of early B-cell ontogeny following stem cell transplant (SCT)\textsuperscript{18}. Previous investigations suggest that the appearance of a secondary MGUS is associated with better outcome\textsuperscript{19,20}. We studied the frequency, characteristics, and natural history of secondary MGUS in MM.

**Methods**

We identified 2088 cases of MM seen at the Mayo Clinic, Rochester, MN between 1/1/1990 and 12/31/2009, diagnosed according to standard criteria\textsuperscript{3,21}. We excluded 62 patients in whom immunofixation was either negative or not obtained within 30 days of diagnosis of MM, 53 with biclonal MM, 3 with amyloidosis, 16 who refused research authorization, and 12 without adequate data. The study was approved by the Mayo Institutional Review Board.

The diagnosis of secondary MGUS required: 1) Current diagnosis of MM, and 2) A new monoclonal (M) protein with heavy and/or light chain immunoglobulin distinct from the initially diagnosed MM. All data were collected by detailed review of medical and laboratory records,
and the Mayo Clinic MM clinical and hematopoietic stem cell transplant databases. The status of MM at time of secondary MGUS occurrence was assessed according to standard criteria.  

Statistical analysis

Two-sided Fisher exact test was used to test for differences between categorical variables. Time to event analysis were done using the Kaplan-Meier method, and survival curves were compared using the two-tailed log rank test. Multivariate analysis was performed using Cox’s proportional hazards model.

Results and Discussion

Frequency of secondary MGUS

We studied 1942 patients diagnosed with MM, with a median follow up of 7 years. A secondary MGUS occurred in 128 (6.6%). Secondary MGUS was more common in patients who had underwent SCT compared to those who had not undergone such a procedure; 104 of 458 patients (22.7%) versus 24 of 1484 (1.6%), respectively, P<0.001. Among patients who were followed at least 4 times over 2 years (n=439), the corresponding rates were 59 of 163 (36.2%) versus 14 of 276 (5%), respectively. Among patients who were followed at least 8 times over 2 years (n=248), the corresponding rates were 33 of 91 (36.2%) versus 12 of 157 (7.6%), respectively.

The median time from diagnosis of MM to secondary MGUS was 12 months (95% CI, 2 months to 63 months). Among SCT patients, a secondary MGUS occurred 12 months or more following transplantation in only 15 patients (14%). The median duration of secondary MGUS was 5.9 months. Of the 128 individuals identified with secondary MGUS, 34 (27%) patients had multiple secondary MGUS’s of varying isotypes.
Characteristics of Secondary MGUS.

Patient characteristics are given in Table 1. Most secondary MGUS M proteins were small; detectable by immunofixation only in 84 patients (66%), 0.2 to 0.9 gm/dL in 29 patients (23%), and 1 gm/dL or greater in 15 patients (12%). Cytogenetic data to classify the underlying MM was available in 107 patients who developed secondary MGUS; 26 patients had hyperdiploidy and 18 patients had an immunoglobulin heavy chain (IgH) translocation (including 9 with t(11;14) and 6 with t(4;14) translocations). In 37 patients results were normal, and 26 had other cytogenetic abnormalities. In most patients (87%), the underlying MM was responsive to therapy at time of secondary MGUS diagnosis.

Survival of MM patients with a secondary MGUS

The median OS of the study cohort was 41 months. OS was significantly superior among patients who developed secondary MGUS compared to the rest of the cohort, 73 months versus 38 months respectively, P<0.001 (Figure 1). On multivariate analysis in a model containing age, International Staging System (ISS) stage, stem cell transplant (yes/no), secondary MGUS, and serum creatinine, the presence of secondary MGUS retained independent prognostic value, P=0.002; all other variables were significant at P<0.001 with the exception of serum creatinine which was significant at P=0.043. Survival was then studied after restricting analysis to patients diagnosed since the year 2000 (n=1088); OS was superior in patients with second MGUS (n=86) versus those without (n=1002), median 77 versus 51 months, respectively, P<0.001. On multivariate analysis, secondary MGUS and date of diagnosis of MM were independently predictive of OS, P<0.001 for both factors.
On landmark analysis at 12 months, OS remained significantly superior in patients who developed secondary MGUS compared to the rest of the cohort, 73 months versus 53 months respectively, P<0.001. A landmark analysis performed 16 months also found similar results, median OS 77 months versus 55 months respectively, P<0.001.

Among patients who did not undergo SCT (n=1484), OS was significantly better in those who developed a secondary MGUS (n=24) versus the rest (n=1460), 49 months versus 31 months respectively, P=0.01. The results were identical when the survival analysis was repeated after deleting patients who had achieved complete response (CR), or CR plus near CR. Among MM patients who underwent SCT (n=458), there was no significant difference in OS in those who developed a secondary MGUS (n=104) versus the rest (n=354), 73 months versus 68 months respectively, P=NS.

Median OS was significantly superior, 94 months versus 62 months (P=0.04), among patients in whom the secondary MGUS was detected more than 12 months after initial diagnosis compared with those in whom the secondary MGUS occurred sooner. Similarly, the occurrence of a secondary MGUS more than 6 months after transplant was associated with better OS, median 102 versus 68 months, P=0.02. On a Cox proportional hazards model, a longer duration of secondary MGUS was associated with significantly inferior survival, P=0.034. Similarly, among patients with secondary MGUS, there was also a trend to better OS in those in whom the MGUS resolved (n=111) compared to those with persistent MGUS (n=17), 81 months versus 48 months respectively, P=0.07.

This study shows that secondary MGUS occurs in approximately 7% of MM, and the occurrence appears several fold higher following SCT compared with patients not undergoing SCT. Since this was not a prospective study in which patients were tested at predefined regular
intervals for the occurrence of a second M protein, the rates of secondary MGUS that we report likely underestimate the true occurrence of this process. Further we are not able to identify new clones that secrete the same M protein type as the MM, but only those which have a different heavy and/or light chain isotype.

Secondary MGUS was a favorable prognostic factor for OS, independent of year of diagnosis, age, stage, and renal function. This is consistent with findings from other studies in SCT patients\textsuperscript{20,23,24}. The failure of a secondary MGUS to spontaneously resolve and the duration of secondary MGUS may affect OS, but this needs further study.
Acknowledgements

Supported in part by grants CA 107476, CA 62242, CA100707, and CA 83724. from the National Cancer Institute, Rockville, MD, USA. Also supported in part by the Jabbs Foundation, Birmingham, United Kingdom and the Henry J. Predolin Foundation, USA.

Author Contribution Statement
Contribution: R.K.W. and S.V.R. analyzed data and wrote the manuscript; D.R.L, A.D., S.K., and H.M.L. contributed to the analysis, provided critical review, and edited the manuscript. All authors reviewed and approved the final manuscript.

Conflict of Interest Disclosure Statement
None of the authors have conflicts of interest pertinent to this manuscript
References:


Table 1. Secondary MGUS patient characteristics

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Median (Range) or No. of patients (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age in years, median (range)</td>
<td>64 (33-83)</td>
</tr>
<tr>
<td>MM Stage at time of secondary MGUS dx, no. of patients (%)</td>
<td></td>
</tr>
<tr>
<td>Non-responsive/Progressive</td>
<td>16 (13)</td>
</tr>
<tr>
<td>Stable plateau</td>
<td>5 (4)</td>
</tr>
<tr>
<td>PR</td>
<td>45 (35)</td>
</tr>
<tr>
<td>VGPR</td>
<td>31 (24)</td>
</tr>
<tr>
<td>NCR</td>
<td>8 (6)</td>
</tr>
<tr>
<td>CR</td>
<td>23 (18)</td>
</tr>
<tr>
<td>Secondary MGUS Ig type, no. of patients (%)</td>
<td></td>
</tr>
<tr>
<td>IgA</td>
<td>7 (6)</td>
</tr>
<tr>
<td>IgM</td>
<td>85 (66)</td>
</tr>
<tr>
<td>IgG</td>
<td>27 (21)</td>
</tr>
<tr>
<td>Light Chain only</td>
<td>9 (7)</td>
</tr>
<tr>
<td>Months from MM diagnosis till onset of secondary MGUS, median (range)</td>
<td>12 months (1-189)</td>
</tr>
<tr>
<td>No. of isotypes of secondary MGUS, no. of patients (%)</td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>94 (73)</td>
</tr>
<tr>
<td>≥2</td>
<td>34 (27)</td>
</tr>
</tbody>
</table>
Figure Legends

**Figure 1. Overall survival all patients.** Median overall survival was 73 months in patients with secondary MGUS versus 38 months in the rest of the cohort, P<0.001.
Figure 1

SecondMGUS: Yes/No
- Secondary MGUS
- No Secondary MGUS
- 1-censored
- 2-censored
Incidence, clinical course, and prognosis of secondary monoclonal gammopathy of undetermined significance in patients with multiple myeloma