original paper

haematologica 2001; 86:1172-1179
http://www.haematologica.it/2001_011/1172.htm

The impact of M-component type and immunoglobulin concentration on the risk of malignant transformation in patients with monoclonal gammopathy of undetermined significance

HENRIK GREGERSEN,* LENE MELLEMKJÆR,°
JENNA SALLING IBSEN,# JENS FREDERIK DAHLERUP,@
LARS THOMASSEN,° HENRIK TOFT SØRENSEN^
*Department of Hematology B, Aalborg Hospital, Aalborg;
°Institute of Cancer Epidemiology, Danish Cancer Society;
#Department of Clinical Chemistry, Aalborg Hospital, Aalborg;
@Department of Medicine V, Aarhus University Hospital;
^Department of Clinical Epidemiology at the Institute of Epidemiology and Social Medicine, University of Aarhus, Denmark

Correspondence: Henrik Gregersen, M.D., Department of Hematology, Aalborg Hospital, Box 561, DK-9000 Aalborg, Denmark.
Phone: international +45.99322326. Fax: international +45.9932351.
E-mail: henrik.gregersen@dadlnet.dk

Background and Objectives. In this study the impact of gender, age, type of M-component and concentration of immunoglobulins on the risk of malignant transformation in monoclonal gammopathy of undetermined significance (MGUS) was assessed.

Design and Methods. We identified 1,247 cases of MGUS in the period 1978 to 1993 in North Jutland County, Denmark. Data on cancer occurrence in the MGUS cohort were obtained from the Danish Cancer Registry. The expected numbers of incident cancer cases were calculated from age-, sex-, county-, and period-specific cancer incidence rates. The impact of the variables mentioned above on the risk of malignant transformation was analyzed in Poisson regression models.

Results. The relative risk of IgA compared to IgG was 1.8 (95% confidence interval, 1.1-3.0), while the relative risk of IgM compared to IgG was 1.1 (0.7-1.9). For all three types of MGUS, the risk of malignant transformation was higher among females than among males, and the risk increased with increasing concentration of immunoglobulin with very high risks for the patients with the highest levels of immunoglobulin. Hypogammaglobulinemia was associated with malignant transformation in patients with IgG type MGUS. For IgG and IgM MGUS, the risk decreased with increasing age and with follow-up beyond one year.

Interpretation and Conclusions. Female sex, IgA M-component type and high concentration of the immunoglobulin comprising the M-component were associated with a high risk of malignant transformation. Hypogammaglobulinemia, young age at diagnosis and short follow-up were risk factors in particular for those with IgG MGUS.

Key words: benign monoclonal gammopathies, multiple myeloma, lymphoproliferative disorders, registries, prognosis.

Monoclonal gammopathy of undetermined significance (MGUS) is the most common immunoglobulin disorder with an estimated prevalence of 3% in people above 70 years of age and 4% in those above 80 years.[1,2] MGUS is characterized by the presence of a homogeneous monoclonal protein (M-component) in the serum of subjects without evidence of multiple myeloma, Waldenström's macroglobulinemia, primary amyloidosis, or other lymphoproliferative disorders.[3] Patients with MGUS have an increased risk of developing symptomatic malignant monoclonal gammopathy, most often multiple myeloma and less frequently another malignant lymphoproliferative disorder.[4,5] The malignant transformation is associated with a shorter survival in MGUS.[4,5]

Data on the impact of M-component type and concentration of the immunoglobulins on malignant transformation in MGUS are conflicting. Three studies have not found any of these variables to be risk factors for malignant transformation.[5-7] However, other studies have found an association between malignant transformation and particular parameters such as IgA type M-component,[4] κ light chain,[8] hypogammaglobulinemia,[9] concentration of the M-component[8,9] and age.[9,10] The major short-

coming of previous studies has been the size of the studies which included 64 to 397 MGUS patients.

In the present study from Denmark, the impact of gender, age, type of M-component and concentration of immunoglobulins on the risk of malignant transformation was analyzed in a large population-based registry of MGUS patients. Poisson regression models, adjusting for the rates of multiple myeloma and malignant lymphoproliferative disorders in the general population, were used to estimate the relative risk of the study variables.

Design and Methods

We conducted the study in North Jutland County, Denmark, which has 490,800 inhabitants (approximately 9% of the total population of Denmark). Every citizen in Denmark is assigned a personal identification number (ID number) at birth, thus enabling linkage between different registries.

Study population

Until 1994 the Departments of Clinical Chemistry at Hjørring and Aalborg Hospitals performed all the serum and urine protein electrophoreses requested by hospital doctors and family doctors in the county. The Microzone Electrophoresis System (Beckman® Instruments Inc., Fullerton, Ca, USA) was used at Hjørring Hospital until 1988, and thereafter the electrophoresis was performed on agarose gel.[11] Agarose gel electrophoresis was used throughout the period at Aalborg Hospital. All sera with a suspected M-component were further examined at Aalborg Hospital by immunofixation using monospecific antibodies from Dakopatts A/S, Copenhagen, Denmark. The immunoglobulins were quantified by nephelometry.

The Department of Clinical Chemistry, Aalborg Hospital, has maintained a registry of all patients in North Jutland County with an identified M-component during the 16-year period 1978-1993. The records contain data on name and ID number, date of detection, type of M-component in serum, and concentration of immunoglobulins. During the study period 2,563 patients with M-components were registered. All the members of this cohort were linked by their ID numbers to the Central Population Register to verify the ID number and to obtain dates of death or emigration. In addition, the 2,563 persons with a detected M-component were linked by their ID numbers to the Danish Cancer Registry.

Hospital departments, family doctors, and practising specialists in Denmark are required to report all incident cases of cancer to the Danish Cancer Registry.[12] Annual links to the Danish Hospital Discharge Registry and the National Death Certificate Files ensure that diagnoses of cancer that have not been reported to the Cancer Registry are subsequently included in the cancer files. Diagnoses are coded according to a Danish version of the International Classification of Diseases, seventh revision (ICD-7), and the completeness and validity of the Registry have been estimated to be 95 to 98 percent.[12]

MGUS classification

We obtained information on the cancer diagnosis, if any, and the date of diagnosis. People with an M-component were classified as having MGUS if multiple myeloma (ICD-7 203.0-203.2), Waldenström's macroglobulinemia (203.3), non-Hodgkin's lymphoma (200, 202), or chronic lymphocytic leukemia (204.0) were not registered before or within 100 days from detection of the M-component. We chose a period of 100 days from a practical point of view, because this interval is sufficient for follow-up investigations such as tissue biopsy and radiological examinations. From 1978 to 1993, 1,324 cases of MGUS were identified. However, this procedure did not permit exclusion of patients with primary amyloidosis or heavy chain disease, two infrequent conditions not consistent with MGUS.

In our study malignant transformation denotes the development of multiple myeloma, Waldenström's macroglobulinemia, non-Hodgkin's lymphoma, or chronic lymphocytic leukemia in MGUS patients. When at least one of the non-monoclonal immunoglobulins were reduced, this was recorded as hypogammaglobulinemia.

Statistical analysis

The follow-up period began 100 days after detection of the M-component, and ended at the date of death, emigration, or December 31, 1995 (latest year of complete cancer incidence data in the Danish Cancer Registry, when the analysis was performed). The cumulative risk of malignant transformation was estimated using the Kaplan-Meier method.[13]

Standardized incidence ratios (SIR) i.e. the ratios of observed-to-expected numbers of cancer were calculated on the basis of age-, sex-, county-, and period-specific incidence rates.[14] National incidence rates for Waldenström's macroglobulinemia were applied due to the low incidence of this malignancy. The 95% confidence intervals for the standardized incidence ratios (SIR) were computed based on the assumption that the observed number of cancers in a specific category followed a Poisson distribution.[15]

In order to make SIR calculations and Poisson regression models comparable, both analyses only included IgA, IgG and IgM patients with complete data, whereas all patients with biclonal and exclusive light chain MGUS were included in the SIR computation. From the 1,324 MGUS patients, 55 (4%) patients with IgA, IgG or IgM type MGUS were excluded due to missing data on concentration of at least one of the immunoglobulins and 22 (2%) were excluded due to missing data on the light chain type leaving 1,247 patients for analysis. Of the 1,247 MGUS patients, 1,178 had IgA, IgG or IgM type MGUS.

Poisson regression models incorporating the age–, sex–, county– and period-specific incidence rates were used to estimate the impact on the risk of malignant transformation of sex, age, type of M-component, concentration of immunoglobulins, hypogammaglobulinemia and length of follow-up.[16,17]

In the Poisson regression model gender (male or female), light chain type (kappa or lambda) and hypogammaglobulinemia (absent or present) were considered as dichotomous variables. The variables age (<70 years, 70-79 years, ≥80 years), type of M-component (IgA, IgG, IgM), concentration of immunoglobulin (low level, intermediate level, high level) and length of follow-up (<1 year, 1-4 years, 5-9 years and ≥10 years) were considered as polytomous variables. The subgroups printed in bold above were used as references in the models. The three levels of immunoglobulin concentration were: low level ≤ 10 g/L for IgA and IgM, <18 g/L for IgG; intermediate level = 10-25 g/L for IgA and IgM, 18-30 g/L for IgG; high level ≥ 25 g/L for IgA and IgM, >30 g/L for IgG. Reference intervals for IgA were 0.8-3.3 g/L, for IgG 8.0-18.0 g/L and for IgM 0.7-3.0 (females 0.3-2.2) g/L.

Ethics

The study was approved by the Regional Ethics Committee (no 2-16-41-2-90 (93/12)), and special approval was obtained from the Danish Data Protection Agency (no 1993-1110-1105).

Results

The MGUS cohort comprised 647 males and 600 females, all together with a median follow-up time of 4.9 years (range, 0-17.7 years), totaling 6,802 person-years at risk. The mean age at diagnosis of MGUS was 68.1 years (range, 10.1-97.4 years). The serum M-component was IgA in 124 cases (9.9%), IgG in 823 (66.0%), IgM in 231 (18.5%), biclonal in 39 (3.1%), and exclusively light chain in 30 (2.4%). In IgA MGUS the median level of IgA was 9.7 g/L (range, 2.0-71.9 g/L), in IgG MGUS the median level of IgG was 15.4 g/L (2.0-114 g/L) and in IgM MGUS the median level of IgM was 7.0 g/L (1.0-65.6 g/L). Hypogammaglobulinemia was present in 329 (26.4%) of the 1,247 patients.

Table 1. Poisson regression model of the impact of sex, age, M-component type, presence of hypogammaglobulinemia and length of follow-up in the combined group of 1,178 patients with IgA, IgG or IgM monoclonal gammopathy of undetermined significance.

Parameter	*No. of patients*	*No. of events*	*Relative risk*	*95% CI*
Intercept			34.5	19.3-61.8
Sex				
Male	614	42	1.0	
Female	564	56	1.5	1.0-2.2
Age				
0-69 years	549	35	1.0	
70-79 years	395	39	0.6	0.4-1.0
≥ 80 years	234	24	0.4	0.3-0.7
M-component heavy chain				
IgG	823	59	1.0	
IgA	124	19	1.8	1.1-3.0
IgM	231	20	1.1	0.7-1.9
M-component light chain				
κ	730	62	1.0	
λ	448	36	1.0	0.6-1.5
Hypogammaglobulinemia				
No	865	50	1.0	
Yes	313	48	2.6	1.7-3.9
Period of follow-up				
< 1 year	1178	26	1.0	
1-4 years	992	44	0.4	0.2-0.6
5-9 years	678	21	0.3	0.2-0.6
≥ 10 years	193	7	0.4	0.2-0.9

The categories printed in bold are references in the regression model. The numbers indicated for follow-up are the numbers of patients at risk at the start of each follow-up period.

During follow-up, 107 cases of malignant transformation were observed versus 6.0 expected, yielding a standardized incidence ratio (SIR) of 17.9 (95% confidence interval, 14.7-21.7). The cumulative risks of malignant transformation at 5, 10 and 15 years of follow-up were 7.7% (6.1-9.4%), 13.0% (10.2-15.7%) and 18.3% (12.4-24.2%), respectively.

The SIR of malignant transformation was 32.0 (19.5-49.5) in IgA MGUS, 16.4 (12.6-21.0) in IgG MGUS and 17.2 (10.5-26.5) in IgM MGUS. In biclonal MGUS, two cases of malignant transformation were observed versus 0.14 expected, giving a SIR of 14.5 (1.6-52.2). In patients with exclu-

Table 2. Poisson regression model of the impact of sex, age, type of light chain, concentration of immunoglobulin containing the M-component, presence of hypogammaglobulinemia, and length of follow-up in 1,178 patients with monoclonal gammopathy of undetermined significance according to type of heavy chain.

	IgA MGUS (N = 124)				*IgG MGUS (N = 823)*				*IgM MGUS (N = 231)*			
Parameter	*No. of patients*	*No. of events*	*RR*	*95% CI*	*No. of patients*	*No. of events*	*RR*	*95% CI*	*No. of patients*	*No. of events*	*RR*	*95% CI*
Intercept			6.8	0.9-49.7			13.9	5.9-32.6			17.0	4.3-68.0
Sex												
Male	70	8	1.0		407	26	1.0		137	8	1.0	
Female	54	11	2.6	1.0-7.0	416	33	1.5	0.9-2.5	94	12	3.2	1.3-8.0
Age at MGUS												
0-69 years	58	5	1.0		389	24	1.0		102	6	1.0	
70-79 years	39	5	0.6	0.2-2.1	280	22	0.5	0.3-0.8	76	12	0.8	0.3-2.2
≥ 80 years	27	9	1.0	0.3-3.1	154	13	0.3	0.2-0.6	53	2	0.2	0.0-0.8
M-component light chain												
κ	71	12	1.0		485	35	1.0		174	15	1.0	
λ	53	7	0.7	0.3-1.7	338	24	1.0	0.6-1.5	57	5	1.5	0.5-4.1
Level of Immunoglobulin												
Low	68	4	1.0		534	12	1.0		143	5	1.0	
Intermediate	47	10	4.0	1.2-13.2	226	23	4.5	2.2-9.1	69	12	5.3	1.8-15.3
High	9	5	13.1	3.1-56.0	63	24	20.2	9.8-41.6	19	3	7.1	1.4-35.7
Hypogammaglobulinemia												
No	75	7	1.0		621	29	1.0		169	14	1.0	
Yes	49	12	1.4	0.5-4.1	202	30	2.1	1.2-3.6	62	6	0.6	0.2-1.7
Period of follow-up												
< 1 year	124	2	1.0		823	18	1.0		231	6	1.0	
1-4 years	101	13	1.6	0.4-7.1	703	26	0.4	0.2-0.7	188	5	0.2	0.1-0.7
5-9 years	71	3	0.7	0.1-4.4	476	11	0.4	0.2-0.8	131	7	0.5	0.2-1.4
≥ 10 years	19	1	1.0	0.1-11.8	135	4	0.5	0.2-1.6	39	2	0.4	0.1-1.8

The categories printed in bold are references in the regression models. The numbers indicated for follow-up are the numbers of patients at risk at the start of each follow-up period. RR denotes relative risk and CI confidence interval.

sively light chain MGUS, only 1 case of malignant transformation was observed versus 0.07 expected, giving a SIR of 14.5 (0.2-80.5).

Figure 1 shows the SIRs of malignant transformation to multiple myeloma and malignant lymphoproliferative disorders, respectively, in MGUS of IgA, IgG and IgM type. The risk of multiple myeloma was particular high in IgA MGUS. In IgM MGUS no case of multiple myeloma was observed whereas the risk of malignant lymphoproliferative disorders was increased.

The impact of M-component type, sex, age, presence of hypogammaglobulinemia and length of follow-up for 1,178 patients with IgA, IgG or IgM MGUS was analyzed in a Poisson regression model (Table 1). We found IgA type M-component, presence of hypogammaglobulinemia, female sex, age less than 70 years and the first year of follow-up to be associated with an increased risk of malignant transformation. There was no association between type of light chain and malignant transformation.

The analysis was stratified on type of M-component with inclusion of concentration of immunoglobulin in addition to the other variables. For IgA MGUS, female sex and high concentration of IgA were associated with malignant transformation (Table 2). For IgG MGUS, age less than 70 years, high concentration of IgG, presence of hypogammaglobulinemia and the first year of follow-up were significantly associated with an increased risk of malignant transformation, while female sex was borderline significantly associated with malignant transformation (Table 2). For IgM MGUS female sex, high concentration of IgM, the first year of follow-up and young age were risk factors for

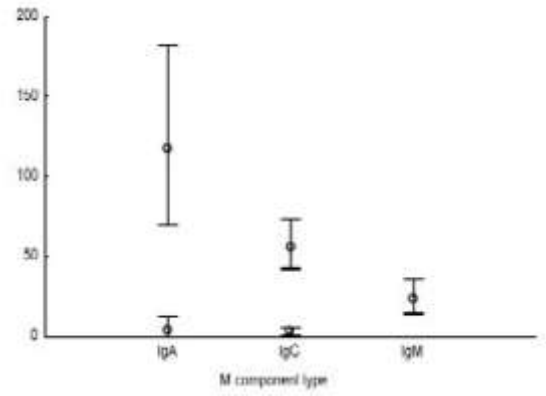

Figure 1. The standardized incidence ratios (SIRs) of malignant transformation in 1,178 patients with IgA, IgG or IgM monoclonal gammopathy of undetermined significance. Closed circles indicate malignant transformation to multiple myeloma and open circles indicate malignant transformation to malignant lymphoproliferative disorders.

malignant transformation (Table 2). Of the 26 cases of malignant transformation in the first year of follow-up, 54% (14/26) were identified in the high concentration category, while the corresponding figures for the 1-4, 5-9 and 10+ years of follow-up were 30% (13/44), 24% (5/21) and 0% (0/7), respectively. Thus, cases with a high concentration of the M-component contributed substantially to the early excess.

Because of the limited number of patients with biclonal and exclusively light chain M-components, these groups were not analyzed in the Poisson regression models.

Discussion

The lack of knowledge about reliable and valid risk factors for malignant transformation in MGUS have led most authors to recommend an indefinite follow-up of these patients. The transformation can occur abruptly after years of observation and an increase of the M-component with time is found to be a strong risk factor for malignant transformation.[18] However, a classification of MGUS patients into low or high risk of malignant transformation could have implications for the intensity of the follow-up.

The present study represents an epidemiological approach to MGUS and the use of Poisson regression models enables a description of the effects on the risk of malignant transformation of several potential risk factors while taking into account the risk in the general population. The definition of MGUS applied is not based on quantitative criteria but on the absence of registration of a malignant monoclonal gammopathy within three months after the detection of the M-component for the first time. Our inclusion criteria are comparable with those used in previous studies concerning the absence of a malignant monoclonal gammopathy but differ in the requirement of an upper limit in the quantification of the M-protein size and the percentage of bone marrow plasma cells used in most studies. In this regard, we cannot rule out that the present MGUS cohort contained more cases of asymptomatic myeloma or indolent lymphoma than shorter series from single institutions. However, it must be emphasized that the distinction between MGUS and asymptomatic or smoldering myeloma can be difficult even when quantitative criteria are applied since both conditions are part of a continuous spectrum of indolent plasma cell disorders. However, it deserves note that, in our study the risk of malignant transformation expressed in terms of cumulative risk was lower than that reported from most other studies.[4,5,7,8,18,19] Thus it is likely that the impact of asymptomatic myeloma on the cohort was comparable to that in other studies. The main advantages of our study are the high completeness and validity of the nationwide Danish Cancer Registry, and the large number of MGUS patients included which increase the precision of the study results. However, when the analysis was stratified on type of M-component there were limited possibilities of exploring the importance of the specific risk factors in respect to IgA and IgM MGUS.

Gender

We found that female MGUS patients had an increased risk of malignant transformation. This finding is unexpected, but it is in accordance with a Dutch study on 334 out-patients with MGUS that found 11 out of 14 patients who developed multiple myeloma were females.[8] The incidence of multiple myeloma is higher in males than in females,[20] and population based studies on the prevalence of MGUS have found a slightly higher number of males than females with MGUS.[1,2] In our study the same pattern with a preponderance of male patients was seen.

Age

In our study, age 70 years or more was associated with a lower risk of malignant transformation than age less than 70 years. This pattern was most pronounced for IgG MGUS. This finding is support-

ed by an Italian study in which, among 22 different variables established at the initial diagnosis of MGUS, only age was significantly and negatively associated with malignant immunoproliferative disease.[10] In contrast to this, a study by Baldini *et al.* found that age more than 70 years in IgG MGUS was associated with an increased risk of malignant transformation.[9] Thus, it remains unsettled whether MGUS in the elderly constitutes a more harmless condition than MGUS in younger people.

M-component type

IgA type MGUS was associated with a higher risk of malignant transformation than IgG and IgM type MGUS. The same was found in an often quoted Spanish study on 128 MGUS patients.[4] Other studies have not found any association between the type of M-component in MGUS and risk of malignant transformation. Multiple myeloma of IgA type is, in clinical practice, often considered more aggressive with a shorter time to progression than IgG myeloma.[21,22] It is possible that MGUS and multiple myeloma of the IgA type share this characteristic of early progression. The risk of malignant transformation in IgA MGUS was not particularly increased during early follow-up as was the case for IgG MGUS, which indicates that the increased risk in IgA MGUS could not be explained by inclusion of asymptomatic cases of IgA multiple myeloma in the cohort.

The Dutch study on 334 MGUS patients found that kappa light chain was a risk factor for malignant transformation.[8] However, as stated by the authors, the finding should be interpreted with caution since a low percentage of kappa chains was found in the matched control group applied in the study. We found no association between M-component light chain type and the risk of malignant transformation.

Immunoglobulin concentration

For all types of MGUS we found a strong association between the concentration of the immunoglobulin containing the M-component and the risk of malignant transformation. The levels of IgA, IgG and IgM determined by nephelometry are known for the majority of the MGUS patients from the start of the study period in 1978 and were used in this study as an estimate of the M-component concentration. With a few exceptions, there is a good correlation between M-component quantification by serum protein electrophoresis combined with densitometry and immunoglobulin quantification by nephelometry.[23]

In multiple myeloma, the concentration of the M-component reflects the burden of malignant plasma cells, and this parameter forms part of the widely used prognostic staging system designed by Salmon and Durie. In MGUS it is also likely that the concentration reflects the quantity of monoclonal cells. Some studies have found that a high concentration of M-components was associated with a high risk of malignant transformation,[8,9] whereas other studies have failed to confirm this association.[4,6] Many studies have excluded MGUS patients with concentrations of IgG over 30 g/L, and IgA and IgM over 25 g/L since these levels have been shown to provide some distinction between MGUS and malignant monoclonal gammopathy at the time of detection of the M-component.[24,25] Other studies have not used any restrictions regarding the concentration of the M-component in their inclusion criteria.[6,8,18] Several cases with high M-components that remain stable have been described.[18] We included MGUS patients with high immunoglobulin levels in order to evaluate the risk of malignant transformation in this subgroup of patients. The study confirms that high concentrations of monoclonal immunoglobulin are strongly associated with malignant transformation especially within a short term follow-up. However, it is worth noting that two thirds of patients with high concentrations of immunoglobulins in our study were never registered with multiple myeloma or malignant lymphoproliferative disorders during the follow-up.

Hypogammaglobulinemia

Hypogammaglobulinemia reflects the impact of the monoclonal clone on the normal antibody production, and this condition is often associated with a high burden of monoclonal cells. Whereas almost all patients with multiple myeloma have reduced levels of uninvolved immunoglobulins, hypogammaglobulinemia has been found in 20-33% of MGUS patients.[4,6,9,18] One quarter of our patients had hypogammaglobulinemia. In an Italian study on 386 MGUS patients, reduction of the uninvolved immunoglobulins was found to be a predictor of malignant transformation.[9] We can confirm this finding but in our study the risk associated with hypogammaglobulinemia seems to be mainly confined to patients with IgG MGUS.

In conclusion, we found that female sex, IgA type M-component and a high concentration of the M-component were associated with malignant transformation in MGUS. Young age at diagnosis of

MGUS, depression of the uninvolved immunoglobulins and short follow-up were also found to be risk factors though most pronounced for IgG MGUS. These findings may have implications for the clinical handling and the frequency of follow-up in these patients.

Contributions and Acknowledgments

HG and LM contributed equally to this work and are primarily responsible for it, from conception to the final manuscript. They are the principal authors. The remaining authors qualified for authorship according to the World Association of Medical Editors (WAME) criteria and have taken specific responsibility for the following parts of the content: JSI and JFD, design of the study and acquisition of data; LT, statistical analyses; HTS, analysis and interpretation of data. Order of authorship. Authors are listed according to a criterion of decreasing individual contribution to the work.

Funding

The study was supported by grants from Nordjyllands Amts Forskningsråd, Det Obelske Familiefond, and the Oncologic Research Unit at Aalborg Hospital.

Disclosures

Conflict of interest: none.

Redundant publications: yes, < 50%.

Manuscript processing

This manuscript was peer-reviewed by two external referees and by Professor Giampaolo Merlini, who acted as an Associate Editor. The final decision to accept this paper for publication was taken jointly by Prof. Merlini and the Editors. Manuscript received May 7, 2001; accepted September 20, 2001.

Potential implications for clinical practice

The results of this study make it possible to classify the role of malignant transformation in patients with MGUS which may have implications for the intensity of follow-up required.

References

1. Axelsson U, Bachmann R, Hallen J. Frequency of pathological proteins (M-components) in 6,995 sera from an adult population. Acta Med Scand 1966; 179:235-47.
2. Saleun JP, Vicariot M, Deroff P, Morin JF. Monoclonal gammopathies in the adult population of Finistère, France. J Clin Pathol 1982; 35:63-8.
3. Kyle RA. Monoclonal gammopathy of undetermined significance (MGUS). Bailliére's Clin Haematol 1995; 8:761-81.
4. Blade J, Lopez-Guillermo A, Rozman C, et al. Malignant transformation and life expectancy in monoclonal gammopathy of undetermined significance. Br J Haematol 1992; 81:391-4.
5. Kyle RA. "Benign" monoclonal gammopathy: after 20 to 35 years of follow-up. Mayo Clin Proc 1993; 68:26-36.
6. Carter A, Tatarsky I. The physiopathological significance of benign monoclonal gammopathy: a study of 64 cases. Br J Haematol 1980; 46:565-74.
7. Pasqualetti P, Festuccia V, Collacciani A, Casale R. The natural history of monoclonal gammopathy of undetermined significance. A 5- to 20-year follow-up of 263 cases. Acta Haematol 1997; 97:174-9.
8. van de Poel MH, Coebergh JW, Hillen HF. Malignant transformation of monoclonal gammopathy of undetermined significance among out-patients of a community hospital in southeastern Netherlands. Br J Haematol 1995; 91:121-5.
9. Baldini L, Guffanti A, Cesana BM, et al. Role of different hematologic variables in defining the risk of malignant transformation in monoclonal gammopathy. Blood 1996; 87:912-8.
10. Pasqualetti P, Casale R. Risk of malignant transformation in patients with monoclonal gammopathy of undetermined significance. Biomed Pharmacother 1997; 51:74-8.
11. Johansson BF. Agarose gel electrophoresis. Scand J Clin Lab Invest 1972; 29(Suppl 124):7-19.
12. Storm HH, Michelsen EV, Clemmensen IH, Pihl J. The Danish Cancer Registry: history, content, quality and use. Dan Med Bull 1997; 44:535-9.
13. Kaplan EL, Meier P. Non-parametric estimation from incomplete observations. J Am Stat Assoc 1958; 53:457-81.
14. Bernett A, Allerhand J, Efremides AP, Clejan S. Long-term study of gammopathies. Clinically benign cases showing transition to malignant plasmacytomas after long periods of observation. Clin Biochem 1986; 19:244-9.
15. Kyle RA, Garton JP. The spectrum of IgM monoclonal gammopathy in 430 cases. Mayo Clin Proc 1987; 62:719-31.
16. Breslow NE, Day NE. Statistical methods in cancer research. Vol. 2. The design and analysis of cohort studies. International Agency for Research on Cancer. Lyon, France: 1987.
17. Breslow NE. Multivariant cohort analysis. Natl Cancer Inst Monogr 1986; 67:149-56.
18. Vuckovic J, Ilic A, Knezevic N, Marinkovic M, Zemunik T, Dubravcic M. Prognosis in monoclonal gammopathy of undetermined significance. Br J Haematol 1997; 97:649-51.
19. Giraldo MP, Rubio-Félix D, Perella M, Gracía JA, Bergua JM, Giralt M. Monoclonal gammopathies of undetermined significance. Clinical course and biological aspects of 397 cases. Sangre (Barc) 1991; 36:377-82.
20. Storm HH, Manders T, Friis S, Bang S. Cancer Incidence in Denmark 1989. Copenhagen, Denmark: Danish Cancer Society; 1992.
21. Weber DM, Dimopoulos MA, Moulopoulos LA,

Delasalle KB, Smith T, Alexanian R. Prognostic features of asymptomatic multiple myeloma. Br J Haematol 1997; 97:810-4.
22. Pasqualetti P, Colantonio D, Collacciani A, Casale R, Natali G. Classification and prognostic evaluation in multiple myeloma. A retrospective study of relationship of survivals and responses to chemotherapy to immunological types, 20 single prognostic factors, 15 clinical staging systems, and 6 morphological classifications. Panminerva Med 1991; 33: 93-110.
23. Rieckenberg M, Collier C, Raymond M, Matthews J. Monitoring of monoclonal gammopathies: rational use of densitometry and rate nephelometry. Clin Biochem 1994; 27:457-61.
24. Møller-Petersen J, Schmidt EB. Diagnostic value of the concentration of M-component in initial classification of monoclonal gammopathy. Scand J Haematol 1986; 36:295-301.
25. Kyle RA, Rajkumar SV. Monoclonal gammopathies of undetermined significance. Hematol Oncol Clin North Am 1999; 13:1181-202.