Monoclonal gammopathy: natural history studied with a retrospective approach

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ABSTRACT

The aim of this study was to examine the natural history of monoclonal gammopathy using a retrospective approach and a long observation period. Protein electrophoresis (PE) and immunofixation (IF) was performed on frozen prediagnosis serum samples from 65 multiple myeloma (MM) and 10 Waldenström's macroglobulinemia (WM) cases. Paraprotein was found in 28% and 46% of the samples from cases using PE and IF respectively. The type of paraprotein was IgA in 33.4% of cases, IgG in 57%, and IgM in 8.5%. Excluding light chain or non-secretory disease, 72 % of MM cases had a prodromal MGUS phase within 10 years of diagnosis MM and WM were preceded by MGUS in at least half of the cases, confirming the premalignant nature of this condition.

Key Words: monoclonal gammopathy of undetermined significance, multiple myeloma, Waldenstöm's macroglobulinemia, natural history.

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The prevalence of monoclonal gammopathy (MG) and the probability of progression from monoclonal gammopathy of unknown significance (MGUS) to malignant disease vary between studies reflecting differences in the populations under examination and, sometimes, referral bias. The incidence of MG clearly increase with age. The largest and most frequently cited survey found the prevalence of MGUS to be 3.2% in persons over 50 years of age and 7.5% in those over 70.[1] Several studies have described the progression rate from MGUS to malignant plasma cell disease. The results differ markedly depending on the population studied and time of follow-up.[2-4] Kyle evaluated prognosis in a large cohort of MGUS cases with the longest follow-up time reported so far and concluded that the risk of progression to MM was 1% per year.[5] In the Kyle series, only the concentration and type of monoclonal protein were independent predictors of progression showing that patients with IgM and IgA paraprotein had an increased risk of developing malignant disease.[5] Several smaller studies showed similar results with a higher probability of progression for IgA type MGUS.[2,6] A population-based retrospective study was conducted for the period of 1976-1997 by Ogmundsdottir *et al.*[7] The study was based on findings of positive electrophoreses, from all laboratories in Iceland carrying out protein electrophoresis, thus covering the entire population of the country which at that time had 270,000 inhabitants. The age-standardized incidence of MG was 10.3 and 8.6 per 100,000 for males and females, respectively. A hematological malignancy had been diagnosed in 29% of the patients at the time of MG detection or within the same calendar year. The remaining 71% had been diagnosed with MGUS. The risk of MGUS progressing to malignant lymphoproliferative disease was 10% after a mean follow-up time of 7.4 years. As shown by several other studies, the risk was significantly greater for the IgA type.

Although several reports have been published on MGUS and the premalignant nature of this condition, no study has explored how frequently malignant plasma cell disorders are preceded by MGUS. The objective of this study was to examine the natural history of monoclonal gammopathy

taking advantage of the opportunity to retrieve samples collected in a large population-based study, several years before the diagnosis of malignant plasma cell disease, in an effort to estimate the proportion of MM and WM cases with a prodromal MGUS phase.

Design and Methods

Study base and samples

The study was approved by the Icelandic National Bioethics Committee and The Data Protection Authority. In 1967, the Icelandic Heart Association (IHA) began a population-based study to evaluate risk factors for cardiovascular disease. Known as the Reykjavik Study, it included individuals from the greater Reykjavik area. The 31,000 participants were selected from the National Registry based on their personal identity number and were all born between 1907 and 1935.[8] Serum samples have been collected from these individuals from once up to six times over the last 35 years.

Data were obtained from the Icelandic Cancer Registry for all MM and WM cases in Iceland since 1955 (1991 for WM) and compared with The Reykjavik Study registry to obtain frozen serum samples. Frozen serum samples were available for analysis from 65 MM and 10 WM cases (one sample for each case) and two controls for each case matched for age, gender and sampling time.

Detection of paraprotein

Protein electrophoresis (PE) using agarose gel was performed on all samples. Immunofixation (IF) was carried out on all case samples and also on those samples from controls that had an indistinct band on PE. Hospital medical records were reviewed for all patients regarding diagnosis, paraprotein type and date of diagnosis.

Data analysis

Frequency of MGUS preceding MM/WM, type of paraprotein and time from sample collection to diagnosis of malignant disease were calculated. The data were further analyzed for subgroups defined according to the time elapsed from sample collection to diagnosis of malignant disease.

Results and Discussion

Prevalence of paraprotein in prediagnosis samples

Figure 1 summarizes the main findings regarding paraprotein prevalence and Ig type.

The mean age at diagnosis of all 75 cases (65 MM/ 10 WM, 36 females/39 males) was 69.9 years (median 70, range: 53-90) and the mean time from sample collection to diagnosis of malignant plasma cell disease was 11.7 years (median 10.54, range: 0.08-31). Four cases diagnosed with MM or WM in the same year as the sample was collected were excluded from further analysis. Of these, 3 cases did not have a detectable paraprotein in the sample, 2 with BJ MM and 1 with IgA type.

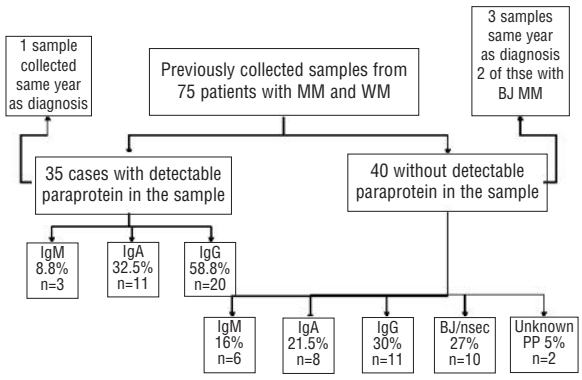

Figure 1. Detection and type of paraprotein in 75 frozen serum samples collected from under one year to 31 years before diagnosis from patients with MM (n=65) and WM (n=10), analysed by immunofixation. For the 40 samples without detectable paraprotein in the previously collected sample the Ig-type is that determined at diagnosis of MM or WM.

PE identified paraprotein in 28% of the 71 samples from cases (n=21, MM=20, WM=1) and 1.3% from controls. IF found paraprotein in 46% of the samples from cases (n=35, MM=32, WM=3) and 2.6 % from controls.

The type of paraprotein detected was IgA in 32.5% of cases, IgG in 58.8 % and IgM in 8.5 %. Only 3 out of the 10 WM cases had a detectable paraprotein in samples collected 3-14 years before diagnosis (mean 7.4 years, median 5.3 years).

Prevalence of paraprotein analysed by time interval between sample collection and diagnosis of MM

As the time interval between serum sampling and diagnosis of MM was expected to influence the likelihood of detecting a prodromal MGUS, the data were analyzed separately for the shortest and longest time interval. In 27 of the MM cases, the sample was collected less than 10 years before diagnosis. In 16 (60%) of these cases, paraprotein was detected in the sample with a mean time from sample collection to diagnosis of 5.3 years (median 5.3, range 1-9.4). IgG was detected in 10 of the cases (63%) and IgA in 6 (38%). Of the 11 MM cases with no detectable paraprotein in a sample collected within 10 years before diagnosis, 4 (31%) had BJ or non-secretory MM (Figure 3). Six patients were diagnosed with MM within 5 years of donating a sample that was negative for paraprotein. Three of these had BJ or non-secretory MM and one patient was recorded as having unknown paraprotein. If only cases with secretory MM or WM are included in the analysis, excluding those with BJ and non-secretory disease, the paraprotein was detectable in 72% of the cases in a sample collected one to ten years before diagnosis.

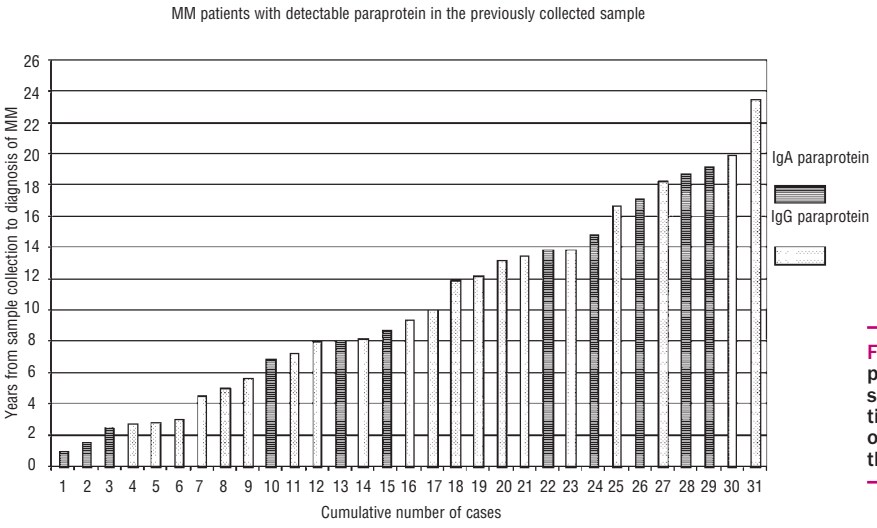

Figure 2. Patients with detectable paraprotein in previously collected sample: time interval between collection of serum sample and diagnosis of multiple myeloma, showing also the type of paraprotein.

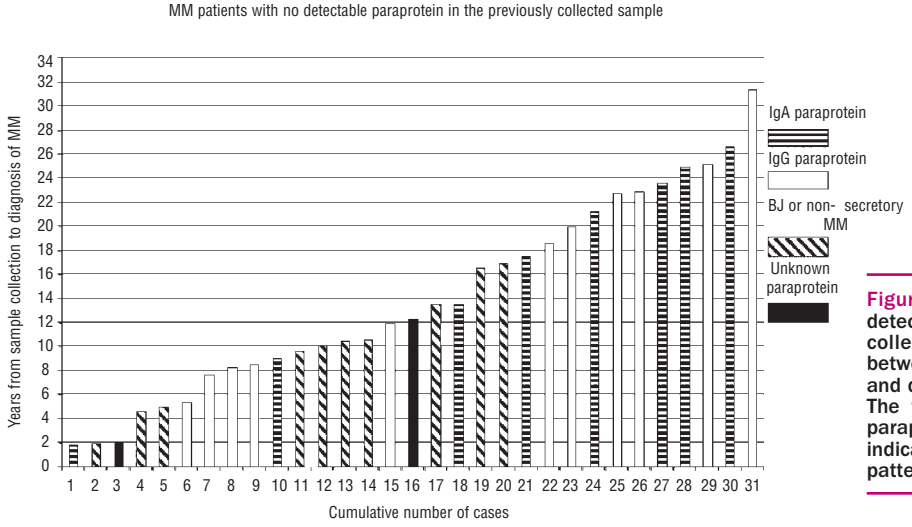

Figure 3. Patients without detectable paraprotein in previously collected sample: time interval between collection of serum sample and diagnosis of multiple myeloma. The type, presence or absence of paraprotein after diagnosis of MM is indicated by the different column patterns.

In twenty patients, the samples available for analysis had been collected more than 15 years before diagnosis of MM. Paraprotein was detected in 7 (35%) of these samples IgG in 4 cases and IgA in 3 cases (Figure 2).

This study is the first of its kind to look at the natural history of MG from a retrospective angle, taking advantage of samples collected 1-31 years before diagnosis of malignant plasma cell disease. This made it possible to estimate the proportion of cases with a prodromal MGUS phase. Multiple myeloma and Waldenström's macroglobulinemia were preceded by MGUS in almost half of the cases up to 23 years before the diagnosis of the malignancy. Since only 28% were detected by PE, IF analysis was required. This shows the importance of using more sensitive methods and explains some of the differences in MG prevalence reported in previous studies. The frequency of MGUS in controls was similar to that reported in several other studies.[1] As would be expected, the prevalence of detectable prodromal MG was higher in samples collected within 10 years of diagnosis.

Of the 6 cases with a negative sample within 5 years of diagnosis, three had light-chain or non-secreting disease. If these cases that were not secreting complete Ig molecules are excluded, more than 70% of MM cases had a prodromal MGUS phase within 10 years of diagnosis. Serum light chain analysis was not available in Iceland at the time of the study. It would be interesting to measure light chains in the old samples from patients with BJ or non-secretory MM since monoclonal light chain prodromal phase is generally thought not to exist. In fact, by definition, MGUS is characterized by detectable whole immunoglobulins in serum. The prevalence of IgA paraprotein in the MM cases with a prodromal MGUS phase was higher than commonly reported in MGUS. This reflects the findings of other

large studies that IgA MGUS has the highest risk of progression to malignant disease.[2,5-7]

Although monoclonal proteins are often incidental findings, and the majority of MGUS do not progress to malignant disease, this study has clearly confirmed the premalignant nature of this condition. Therefore, all these patients should be regularly followed with special emphasis on IgA MGUS cases.

Authors' Contributions

HS: data management, protein electrophoreses, writing of manuscript; VH: data management, writing of manuscript; IO: supervision of protein electrophoreses and immunofixation; VG: supervision of samples collected by The Icelandic Heart association; HO: supervision of data management, writing of manuscript.

Conflicts of interest

The authors reported no potential conflicts of interest.

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