Familiality of benign and malignant paraproteinemias. A population-based cancer-registry study of multiple myeloma families

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Background and Objectives. The occurrence of two or more cases of multiple myeloma (MM) in the same family has been reported from time to time. The current study is the first population- and cancer-registry-based survey to investigate familiality of premalignant or malignant B-cell proliferation.

Design and Methods. A family registry of 218 multiple myeloma cases was compared with the records of the Icelandic Cancer Registry in order to analyze the pedigrees for the occurrence of families with multiple cases of paraproteinemia and hematologic malignancies.

Results. The relative risk of developing monoclonal gammopathies of unknown significance (MGUS) was not increased among first-degree relatives of MM patients, but there was a significantly increased risk of developing MM for females separately (RR = 3.23, CI 1.17-7.01) and for males and females combined (RR = 2.33, CI 1.12-4.26). Analysis for all hematologic malignancies showed an increased risk for female relatives of MM patients (RR = 1.95, CI 1.10-3.20). Eight families were identified in which the propositus with MM had > 1 relatives with MGUS and > 1 with another hematologic malignancy, including 4 families with another relative with MM. In three families both myeloid and lymphoid malignancies occurred.

Interpretation and Conclusions. Although inheritance does not appear to be a major risk factor for the development of paraproteinemias a significant risk of developing MM was found for female relatives. The occurrence of multiple cases of benign and malignant paraproteinemias in a few families does suggest a hereditary contribution. Further studies of such families might reveal clues on pathogenesis.

Key words: paraproteinemia, familiality, MGUS, multiple myeloma, Waldenström's macroglobulinemia.

Haematologica 2005; 90:66-71

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Over many decades there have been occasional reports of two or more cases of multiple myeloma (MM) occurring in the same family,[1-3] raising speculations about possible hereditary factors. Several of these reports are anecdotal observations, many of them including literature surveys of similar families.[4-6] According to the most recent of these surveys around 70 families have been reported with two or more cases of MM in the same family.[6] Approximately 100 families with multiple cases of monoclonal gammopathy of unknown significance (MGUS) and Waldenström's macroglobulinaemia (WM) with or without MM have also been reported.[7-9] One Icelandic family with five affected members, one with MM, three with MGUS and one with WM, has been described.[10-12] A number of studies have been performed searching for paraproteins in relatives of MM, WM or MGUS patients (reviewed by Ögmundsdóttir).[13] Nadeau *et al.*[1] found one additional relative with asymptomatic paraproteinemia in a family with three cases of MM Meijers *et al.*[14] studied a family revealing three patients with MM and three cases of MGUS (IgG and IgA), starting from a proband with MGUS. Eight families with familial MM were described by Maldonado and Kyle[2] and in two of these a total of five cases of IgG or IgA MGUS were found. In the most recently described family with multiple cases of MM the proband with MM had two siblings with MM and two with MGUS and a daughter with acute lymphocyte leukemia.[6] The two MGUS cases were identified after investigation of 19 non-symptomatic family members. Following the initial finding of familial occurrence of WM in two families, Seligman *et al.*[15] stud-

ied relatives of 65 patients and identified 7 families with IgM paraprotein in two or three members. A family study by Linet *et al.*[16] revealed two cases of IgM MGUS among the first degree relatives of 65 WM patients. Spengler *et al.*[17] took the approach of investigating clinical and family histories of 250 patients with a laboratory diagnosis of paraproteinaemia. They were able to test relatives of 22 of these patients and found four families with co-occurrence of MM, MM and MGUS or WM and MGUS. Williams *et al.*[18] were the first to perform a case-control study on 33 probands with MGUS, lymphoma, WM or MM and identified 4 families with one or more relative with MGUS among the case families but none in the control families. Youinou *et al.*[8] studied the relatives of 37 probands with MM, WM or MGUS and found 4 families containing further cases of WM or MGUS. Extensive investigation of relatives of 12 subjects with MGUS identified 3 new cases in 2 families.[19] Summarizing the results of these family surveys, it can be said that a systematic search for paraproteins among relatives of patients with benign or malignant monoclonal gammopathy reveals familial occurrence in approximately 10% of them. A hospital-based case control study for family history (by interview and medical records) involving 439 MM patients did not demonstrate a statistically significant familial risk of MM, but a family history of hematologic malignancy (ICD9 200-208) was associated with a significant relative risk of 2.4 for MM.[20] Eriksson and Hållberg[21] performed a population-based case-control study on 239 Swedish MM patients and found a relative risk of 5.64 (CI 1.16-27.51) of MM among first degree relatives. A more recent population-based case-control interview study of 565 subjects with MM found a significant association with reported family history of MM (3.7) and hematolymphoproliferative cancer (1.7) but no association with other types of cancer.[22]

In a large prospective French study covering 104 centers, 4 cases of familial MM were identified among 1263 MM patients, giving a frequency of 3.2 per 1000.[23] Based on an annual incidence rate for MM of 3 per 100,000 the authors estimated the incidence of familial MM to be 1 per 10^7 per year.

None of these studies can adequately answer the question of how important heredity is in the pathogenesis of benign or malignant paraproteinemias on a population basis. The frequency of familial gammopathy was only addressed in a study by Axelson and Hällén in 1967[24] who identified 3 families with multiple cases of MGUS in their population survey including almost 8000 persons. Data from the comprehensive Swedish Family-Cancer Database show a calculated standardized incidence ratio of 4.25 for MM among offspring of 61-year olds or younger whose parent presented with MM.[25]

The current study is the first survey for familiality of pre-malignant or malignant paraproteinemias that uses a population-based cancer registry. The incidence of multiple myeloma (ICD-10 code C90) in Iceland is similar to that in other European countries: the age-standardized rate for males is 3.5 per 100,000 and for females it is 2.6 per 100,000. The age-standardized incidence rates for hematologic malignancies generally (ICD-10 codes C81-C96) are 21.4 per 100,000 and 13.6 per 100,000 for males and females, respectively. The recently established MGUS registry showed an age-standardized incidence rate of less than 10 cases per 100,000 subjects under 50 years of age, increasing with age from 11 and 17 per 100,000 among at 50-54 year olds to 169 and 119 per 100,000 among 80-84 year olds, for males and females, respectively.[26] This registry is based on laboratory records from an unselected population. We have now compared a family registry of 218 multiple myeloma cases with the records of the Icelandic Cancer Registry for hematologic malignancies and the MGUS registry. The main aim was to estimate the population-based risk of familial paraproteinemias and secondly, to analyze the pedigrees for the occurrence of families with multiple cases of paraproteinemias and hematologic malignancies.

Design and Methods

Population and record linkage

The population of Iceland in 1999 was 277,184 persons (138,783 males and 138,401 females). The Icelandic Cancer Registry (ICR), which is population-based, was started in 1955, at which time the population was 154,613 (77,808 males and 76,805 females). In 1952 the systemic record of the whole population of Iceland was started. This has a unique identification number for each member of the population which has facilitated record linkage studies.

Monoclonal gammopathy database

In collaboration with Icelandic hematologists an effort was made to strengthen the Cancer Registry's database on pre-malignant hematologic disorders. Information on all patients with confirmed monoclonal gammopathy was obtained from the records of the laboratories of the four main hospitals in Iceland. Serum electrophoresis was started in Iceland in 1976. From 1976 to 1994 the electrophoreses were done using the cellulose agarose method. In the period between 1994 to 1997 the four laboratories changed over to the more sensitive high resolution agarose gel method. A database on monoclonal gammopathy was thus established and first described by Ögmundsdóttir *et al.*[26] The database covers a twenty-

two year period, from the beginning of 1976 to the end of 1997. By comparison with the Icelandic Cancer Registry, patients who had been diagnosed with a hematologic malignancy including Waldenström's macroglobulinemia (ICD-10 code C81-C96) were identified, although it must to be noted that Waldenström's macroglobulinemia was only included as a separate entry since 1991. All patients who were not diagnosed with a paraprotein-related malignancy before identification of a monoclonal gammopathy or within the same calendar year were defined as having MGUS, classified as D47.2 according to the ICD-10. A morphological diagnosis is required for entry into the ICR in general. For hematologic malignancies a diagnosis is obtained from a hematologist, based on a bone marrow aspirate. For the diagnosis of multiple myeloma and Waldenström's macroglobulinaemia a specific serum electrophoresis pattern is required as well as a bone marrow aspirate. Icelandic hematologists have used the Salmon and Durie criteria for multiple myeloma since 1977.[27] The diagnosis of WM is based on a monoclonal IgM on serum electrophoresis and the identification of a specific cellular morphology in bone marrow or other tissue sample.

Familiality studies of MM, MGUS and other hematologic malignancies

The ICR produced a list of all patients diagnosed with MM from 1 January 1955 to the end of 1989 and the families of these 218 patients were traced by the Genetic Committee of the University of Iceland. Relatives were checked in the Icelandic Cancer Registry until the end of 1999. Each patient was a proband and each family was traced to the proband's grandparents. All the grandparents' descendants who were 1st, 2nd and 3rd degree relatives of the proband were included in the family. This resulted in some overlapping between families, which was done in order to obtain unbiased representation of the population. The risk of being diagnosed with a hematologic malignancy (ICD-10 code C81-C96) or MM specifically (ICD-10 C90) relative to the population was estimated for each degree of relatedness. The ICR produced incidence figures for the whole population stratified according to gender, age (5-year intervals) and calendar time (5-year intervals).

The risk-years for relatives were stratified in a similar manner and furthermore according to degree of relatedness to the proband using the MANYRS program.[28] For each of these strata the observed number of cases was counted and the expected number was calculated as the product of the incidence and risk-years. The sums of observed and expected numbers were then obtained. Using the database for monoclonal gammopathy the same type of calculation was performed for the risk of MGUS (ICD-10 code D47.2) in relatives of MM patients. Four types of families with MM associated with MM, MGUS or other hematologic malignancy were specifically defined: (i) > 2 cases of MM; (ii) one case of MM with at least one case of MGUS and one case of another hematologic malignancy; (iii) one case of MM with at least one case of MGUS and (iv) one case of MM with at least one case of another hematologic malignancy. In ten families the proband was a patient with plasmacytoma.

Table 1. Relative risk of developing MGUS, multiple myeloma or hematologic malignancies* for first degreee relatives of patients with multiple myeloma.

	Number Obs.	*Number Exp.*	*Ratio O/E*	*95% conf.int.*
MGUS				
Male	2	2.67	0.75	0.08-2.68
Female	2	2.48	0.81	0.10-2.90
Both	4	5.15	0.78	0.23-2.00
Multiple myeloma				
Male	4	2.44	1.64	0.44-4.17
Female	6	1.86	3.23	1.17-7.01
Both	10	4.10	2.33	1.12-4.26
Hematologic malignancy				
Male	13	11.88	1.09	0.59-1.86
Female	15	7.70	1.95	1.10-3.20
Both	28	19.58	1.43	0.96-2.06

**Including multiple myeloma. This table includes entries in the Icelandic Cancer Registry under ICD-10 numbers C81-C96. Waldenström's macroglobulinemia was not registered as a malignant disease until 1991.*

Results

Family associations of MGUS and MM

Table 1 shows a statistical analysis based on pedigrees traced to the 3rd degree of relatedness for 218 patients diagnosed with MM between 1955 and 1989. It can be seen that the relative risk, compared with that of the Icelandic population, for relatives of MM patients developing MGUS was not increased but there was a significantly increased risk of developing MM for females separately and for males and females combined. When all hematologic malignancies were included in the analysis only female relatives of MM patients had a significantly increased risk. It should be noted that WM was not registered as a malignancy until 1991. Before that time patients with WM were sometimes recorded as having lymphomas in cancer registries. For this reason it was not possible to analyze the risk for WM separately. The table only shows results for 1st degree relatives as no significant increase in risk was found for 2nd or 3rd degree relatives for any of the diseases (*results not*

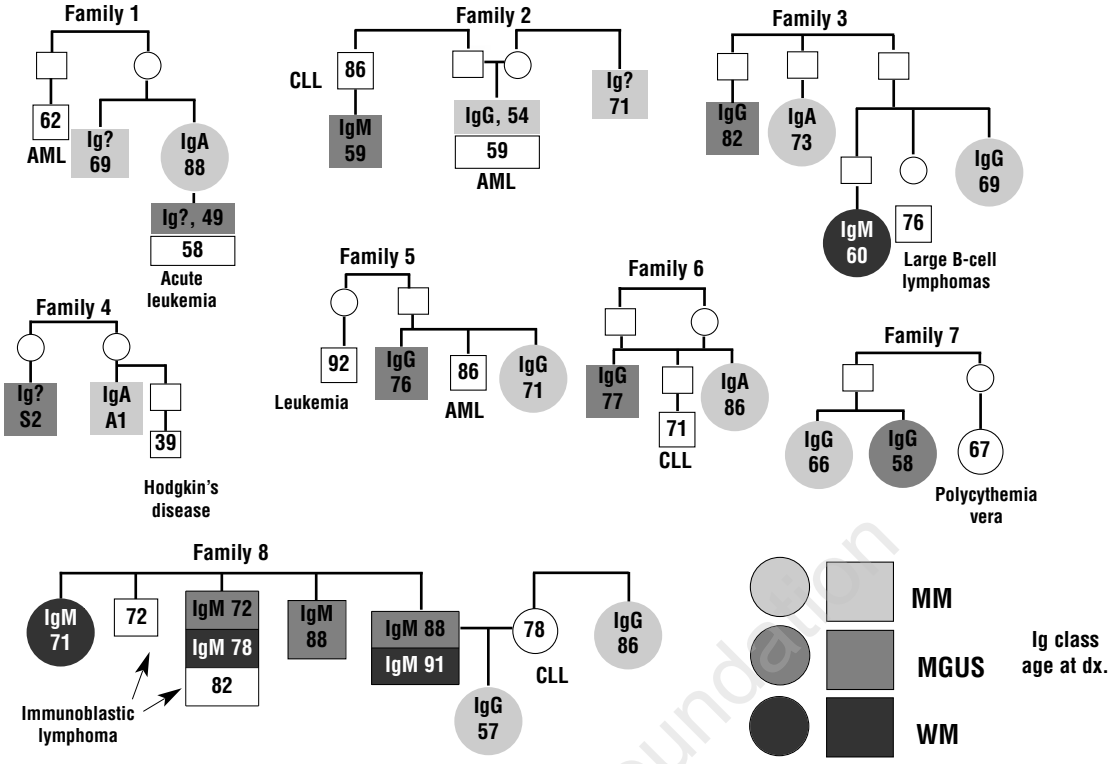

Figure 1. Pedigrees of eight families with multiple myeloma (MM), monoclonal gammopathy of undetermined significance (MGUS) and ≥1 further case of MM, MGUS or ≥1 case of another hematologic malignancy.

shown). In conclusion, there is not an overall familial association between MGUS and MM.

Families with MM, MGUS and other hematologic malignancies

Out a total of 218 probands with MM, 24 had one relative with MM. Of these 14 were among the 218 probands and 10 were diagnosed after 1989 until the close of the follow-up at the end of 1999. Nineteen probands had at least one relative with MGUS, WM occurred in 10 families and a further 58 families had another family member with a hematologic malignancy. On the basis of this information, 8 families were identified in which the proband with MM had one or more relatives with MGUS and one or more relatives with another hematologic malignancy, including 4 families with another relative with MM. This gives an estimate of 4% (95% C.I. 1.7-7.7). The pedigrees are presented in Figure 1. They are considerably abbreviated and therefore do not show that many of the sibships are large (many more than 5, some up to 15). One of these families (# 8) is the family described in our previous studies.[10-12] The Ig class was not identified in the oldest cases but, as far as this information is available, IgA paraprotein occurred in 4 families, IgG was found in 5 families and IgM in 3 families. Although the presence of IgM paraprotein in three siblings in family #8 is very striking it cannot be said that there was any pattern to the Ig class found in each family. Two subjects in family #8 showed progression from MGUS to MM or WM, ending in one case in an immunoblastic lymphoma. In three families (#1, 5 and 7) cases of myeloid as well as lymphoid malignancies occurred. In family #8 the youngest MM patient has relatives with MGUS, WM or MM in both sides of her family. Another branch of that family, traced to common grandparents with the sibship shown, contains one more MM patient, 6 cases of acute or chronic lymphocytic leukemia as well as one each of chronic myeloid leukemia and acute myeloid leukemia. A parent-child relationship between patients was not common in these families. There was a female preponderance among the MM cases in these families (8 females and 4 males) whereas male cases of MGUS far outnumbered female ones (9 to 1) and males were also more common among relatives with other malignancies. The mean age at diagnosis was the same for MGUS and MM, 73.1 and 72.6, respectively. MM occurred in two generations in only two of the families (#2 and 8) and in both cases the patient in the second generation was much younger.

Discussion

The present study shows that female relatives of MM patients have a significantly increased risk of developing MM or another hematologic malignancy. In addition, eight families were identified with multiple cases of MM, MGUS and/or other hematologic malignancies, including one previously reported family.[10-12] Three previous reports calculating familial risk of MM were case-control studies and showed a significant risk associated with hematologic malignancies[20] or MM separately[21,22] of similar magnitude.

As described in the introduction, based on reports in the literature, it was estimated that a systematic search for paraproteins in relatives of MM, WM or MGUS patients would identify familial occurrence of these disorders in approximately 10% of families. On the basis of this estimate we might have expected to find close to 20 families with multiple cases of MM, WM or MGUS. There are several possible reasons for the apparently low number of families that we did actually identify. The diagnosis of MGUS was made purely as a routine laboratory finding and no relatives were tested specifically except for those in family #8. The results of previous studies were based on active testing of relatives, which may have lead to higher detection rates. It is also likely that some cases of MGUS were missed during the period from 1976 to 1994 when the less sensitive cellulose agarose method was used. WM was certainly underestimated as this disease was not regarded as malignant and not included in cancer registries until 1991.

A comparison with other reported families shows that large sibships and relatively advanced age at diagnosis are common features.[2,9,14,15] If a hereditary factor is implicated this would suggest limited penetrance. Some of the early studies appeared to show that families could be divided into two groups, those with IgM MGUS and WM and those with IgG or IgA MGUS and MM.[8,14] The co-occurrence of M and A/G paraproteins in the same family has, however, been noted by previous authors.[17,30] It is thus possible that the aberrant clonal expansion can occur before or after the Ig class switch on the same genetic background although the subsequent chromosomal changes are different.[31]

The co-occurrence of lymphoid and myeloid malignancies in the same family was seen in three of the families and a link to a family with both lymphoid and myeloid leukemias was noted for family #8. Most of the reports in the literature have concentrated on paraproteinemias and immunoglobulin abnormalities.[2,8,9,15,16] The study by Eriksson and Bergström[29] took a wider perspective and found 36 families with two or more cases of malignant blood diseases. A large majority (n=31) of these families had lymphoid malignancies; in 6 of them the relative of the proband with a lymphoproliferative disease had polycythemia vera or myeloid leukemia. A case/control study done by Shpilberg *et al.*[30] showed a significant odds ratio of 3.62 for the occurrence of hematologic malignancies among relatives of 189 patients with various types of such diseases.

The statistical analysis revealed a significant risk of developing MM among female relatives only and in the eight pedigrees female patients with MM were more common whereas most of the MGUS cases were males, possibly implying a greater risk of malignant progression in females. The mean age of MM and MGUS patients in these 8 families was the same, perhaps not unexpectedly in the light of our previous observation that progression from MGUS to malignancy most often occurs within three years of detection.[26] The phenomenon of anticipation, describing earlier age of onset of a genetic disease in successive generations, has been reported for MM and WM[32] and chronic lymphocytic leukemia.[33] Families #2 and 8 in our study support this notion.

Finally, it may be speculated whether families with multiple cases of paraproteinemias can provide clues on pathogenic mechanisms. The possibility of shared environment should always be kept in mind but becomes less likely when several generations and branches of a family are involved. Anticipation may point to certain genetic mechanisms.[32,33] Occurrence of diseases of both lymphoid and myeloid origin may indicate a defect at the level of the hematopoietic stem cell. The higher risk of developing MM for female relatives could point to the contribution of genes on the X chromosome known to be involved in the regulation of B-cell responses and Ig production.[34,35] Interestingly, DNA amplifications involving the X chromosome are observed in a high proportion of patients with mediastinal B-cell lymphoma, a malignancy predominantly diagnosed in females.[36] Family #8 was the subject of our previous studies in which we tested samples from disease-free relatives in three generations below the sibship depicted here. Enhanced B-cell survival after mitogen-stimulation in culture was demonstrated in several family members and this was associated with prolonged expression of BCL-2.[11,12] In conclusion, although inheritance does not appear to be a major risk factor for the development of paraproteinemias, female relatives did have a significant risk of developing multiple myeloma. The occurrence of multiple cases of benign and malignant paraproteiaemias in a few families does suggest a hereditary contribution. Further studies of such families might reveal clues on pathogenesis.

HMÖ: created the idea, directed the work and wrote most of the paper; VH, GMJ: clinical hematologists, provided information about patients and contributed substantially to discussions and writing the paper; GO, KB: provided all information from the Icelandic Cancer Registry, performed all work on genealogy; SD: did the statistical calculations; HT: director of the Icelandic Cancer Registry contributed epidemiological expertise. The authors declare that they have no potential conflicts of interest.

Manuscript received November 14, 2004; accepted November 28, 2004.

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