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Familial Myeloma: Study of a Unique Family

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Summary

We describe a family with five cases of multiple myeloma , three cases of monoclonal gammopathy of undetermined significance (MGUS), and five cases of prostate cancer in two generations. The putative progenitor has progeny with prostate cancer, multiple myeloma, and MGUS with two separate female partners.

Introduction

Multiple myeloma accounts for approximately 10 percent of all hematologic cancers and is most frequent in persons over the age of 65; only 2 percent of patients are younger than 40 years of age.[1–3] The characteristic feature of the disease is a clonal proliferation of malignant plasma cells, which produces a monoclonal protein (M protein) and causes lytic bone lesions. Multiple myeloma can evolve from monoclonal gammopathy of undetermined significance (MGUS), but the factors that contribute to the evolution of MGUS into multiple myeloma are unknown.[4] Extensive chromosomal abnormalities are detectable in the plasma cells from most cases of multiple myeloma, and similar changes are also present in MGUS.

MGUS usually presents a serum M protein of less than 30g/liter and less than 10 percent bone marrow plasma cells. It is differentiated from multiple myeloma by the absence of renal failure, anemia, and bone lesions.[5] IgG is the most common isotype of the M protein in MGUS.[6]

The cause of multiple myeloma is unknown.[2,3] A small but unknown fraction of patients have familial disease. There is evidence of a higher incidence of the disease in African Americans than in whites.[7] In a recent study of 39 families with multiple cases of multiple myeloma, some family members manifested MGUS, other types of hematologic malignancies, or solid tumors.[8] We report an African American family in which there were five cases of multiple myeloma, three of MGUS, and five of prostate cancer.

Materials and Methods

This study was approved by the Institutional Review Board at Creighton University. Our multiple myeloma-prone family was studied at the University of Arkansas for Medical Sciences and Creighton University School of Medicine. The methods for developing the family pedigree are the same as those used in our previous study.[8] A detailed genealogic compilation of this family's medical history, using questionnaires and personal interviews that covered cancer at

all anatomic sites, with pathological confirmation whenever possible, was obtained. Offspring and siblings of myeloma-affected family members were recruited for evaluation of MGUS, along with first-degree relatives of the identical twin of a myeloma-affected family member. A family information service[9] was organized with the assistance of key family members. Twenty blood relatives attended; also present were four of the authors (HTL, ST, KF, JFL). During this one-day visit, the family was educated about multiple myeloma with particular attention to its epidemiologic and genetic risk factors. They were told about the pertinent aspects of our investigation, and consenting first-degree relatives of a myeloma-affected family member provided fresh urine and blood samples to investigate the possibility of MGUS.

Serum and urine protein electrophoresis (SPE, UPE) was performed with the Paragon electrophoresis system and an Appraise densitometer (Beckman Coulter, Inc., Fullerton, CA) using agarose gel (1.0 percent) in 1.2 percent barbital buffer (pH 8.6) on flexible plastic backing. Gels were stained using Paragon Blue: 0.5 percent (w/v) 8-amino-7-(3-nitrophenylazo)-2-(phenylazo)-1-naphthol-3,6-disulfonic acid disodium salt in 5 percent acetic acid solution, as supplied by Beckman Coulter, Inc. Urine samples were concentrated to >100x using a Minicon concentrator **(**Millipore Corporation, Billerica, MA). Protein immunofixation electrophoresis on serum or urine was performed using the gels provided with the Paragon electrophoresis system and consisted of 1.0 percent agarose in a 1.2 percent Tris barbital aspartate buffer. Antisera used were goat IgG fractions, against human IgG, IgA, IgM, kappa and lambda light chains (Beckman Coulter, Inc.). After electrophoresis and fixation on the gel, the proteins were stained with Paragon Blue. Procedures were used as specified in the manufacturer's instructions after validation in our laboratory.[13] All of the tests described above were performed in the Special Chemistry Laboratory at Creighton Medical Laboratories. Serum kappa and lambda free light chains were measured by ARUP Laboratories (Salt Lake City, Utah) using a standard method.[14]

The number of cases meeting the criteria for MGUS in this family was compared with the expected number of cases, which was calculated from published age- and sex-specific prevalence estimates.[6] Figures for Olmsted County, Minnesota,[6] were multiplied by three based on the observation of a three-fold prevalence in African American over white patients in a large series.[7] As rates for persons under the age of 50 years are not available, in this study we used rates for 50 to 60 year olds for the younger age groups. The prevalence in Ghanaian men is twice that in white men,[12] supporting our expected number as conservative. Assuming that the prevalence is lower in younger persons, this approach will overestimate the expected number of cases and thus produce a more conservative statistical test. The observed number was compared with the expected number using the approximate Poisson test of Byar.[13]

Results

Table 1 shows the results for 11 first-degree relatives who were evaluated for MGUS using the free light chain test. In a cohort of this size with this distribution of age and sex, less than one (0.7) MGUS case would be expected, whereas we found three cases. M proteins were also found by SPE patterns in these three family members (III-1, III-6, and II-11), and were characterized by immunofixation as IgG-lambda in III-1, IgG-kappa in III-6, and IgG-lambda in family member II-11. The M proteins in family members III-1 and III-6 were very small, and quantitation was not possible. For family member II-11, the monoclonal band was larger (7.8g/liter), and was accompanied by a reduction in the other gamma globulins (2.4g/liter). Figure 1 shows results of assays for serum free light chain. Urine studies of all 11 individuals tested yielded no evidence of M proteins or monoclonal free light chains.

The pedigree (Figure 2) shows the five family members with multiple myeloma and three with MGUS. Case I-2 is the putative progenitor. He died of colon cancer at age 88 years. However,

he had progeny with multiple myeloma with two separate female partners, namely II-12 with his first partner and II-1, II-5, and II-8 with his second partner. In the third generation, the proband (III-3) had multiple myeloma, whereas two others had MGUS. All of these family members were in the direct line of descent from the putative progenitor. Case II-2 died at age 50 years of pancreatic cancer and her identical twin had multiple myeloma. She is a putative obligate gene carrier, an assumption reinforced by the fact that she has a daughter (III-6) with MGUS. Prostate cancer was found in II-8 at age 69 years, and at age 72 years was also found to have multiple myeloma. That man's brother, II-11, had prostate cancer at age 64 and MGUS at age 73 years. Case II-11 has two sons, III-19 and III-20, who received the diagnosis of prostate cancer at 44 and 41 years, respectively.

Discussion

Our interest in familial multiple myeloma began when we initially investigated a separate family that included a sibship of seven, of whom three had known multiple myeloma and later two more developed MGUS.[14] Of note, one sibling had two primary cancers (prostate cancer and MM) and one sibling with MGUS developed systemic amyloidosis; the father of this remarkable sibship also had prostate cancer.[8] These observations led us to investigate a larger series of familial multiple myeloma with the intent of generating hypotheses relevant to its heterogeneity and genetic transmission.[8]

The overall risk of multiple myeloma in first-degree relatives of multiple myeloma patients is reported to be increased two- to four-fold.[15] Hematologic and solid cancer risks also appear to be higher in relatives of multiple myeloma patients,[8] especially chronic lymphocytic leukemia and non-Hodgkin lymphoma,[4] as well as prostate cancer and endometrial cancer.[8,14,16,17] Brown et al.[18] also have reported an increased risk of multiple myeloma associated with a family history of any hematologic cancer (odds ratio [OR] = 1.7) but did not find a significant increase for solid cancers in both white and black US families. Eriksson and Hallberg,[16] however, in a smaller study of Swedish families with various malignancies, identified an increased risk of prostate cancer in first-degree relatives of patients with multiple myeloma (RR = 3.11)[16]

Evidence of an increased risk of multiple myeloma in relatives of carriers of *BRCA1* or *BRCA2* mutations has also been reported.[19] In addition, Dilworth et al.[20] described a melanoma-prone family wherein a germline mutation of the *CDKN2A* (*p16*) gene was identified in a patient with multiple myeloma. To determine whether the *CDKN2A* mutation was responsible for multiple myeloma, these investigators searched for loss of heterozygosity and they found that the wild-type *CDKN2A* allele was lost in the malignant plasma cells, suggesting that germline mutation of *CDKN2A* may confer an increased susceptibility for multiple myeloma as well as a predisposition to melanoma and pancreatic cancer.[21]

In conclusion, this myeloma-prone family merits long-term medical and genetic follow-up, including formal linkage analysis, in search for a cancer susceptibility locus.

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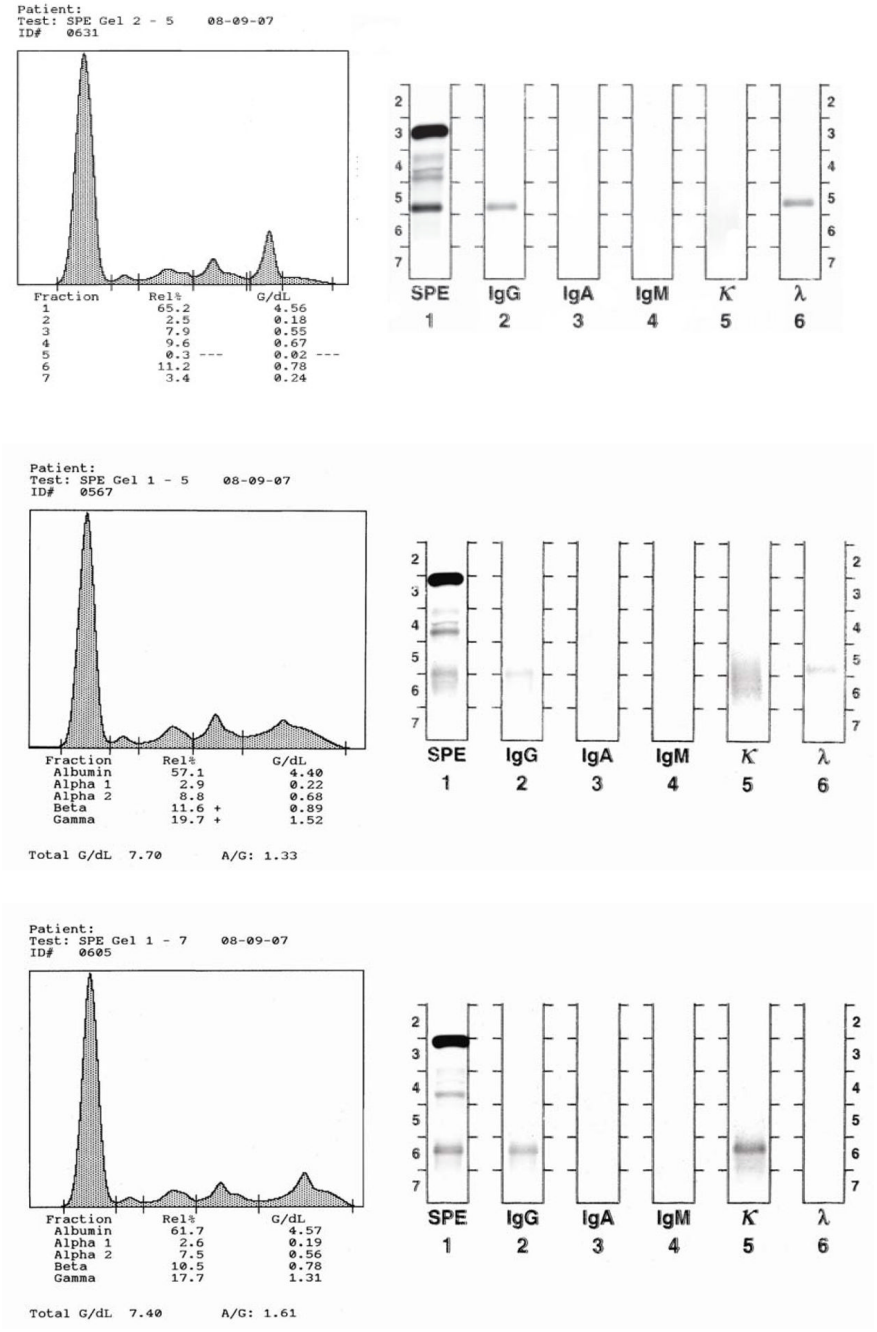

Figure 1.
Serum protein electrophoresis and serum immunofixation documenting three new cases of MGUS in unaffected family members.

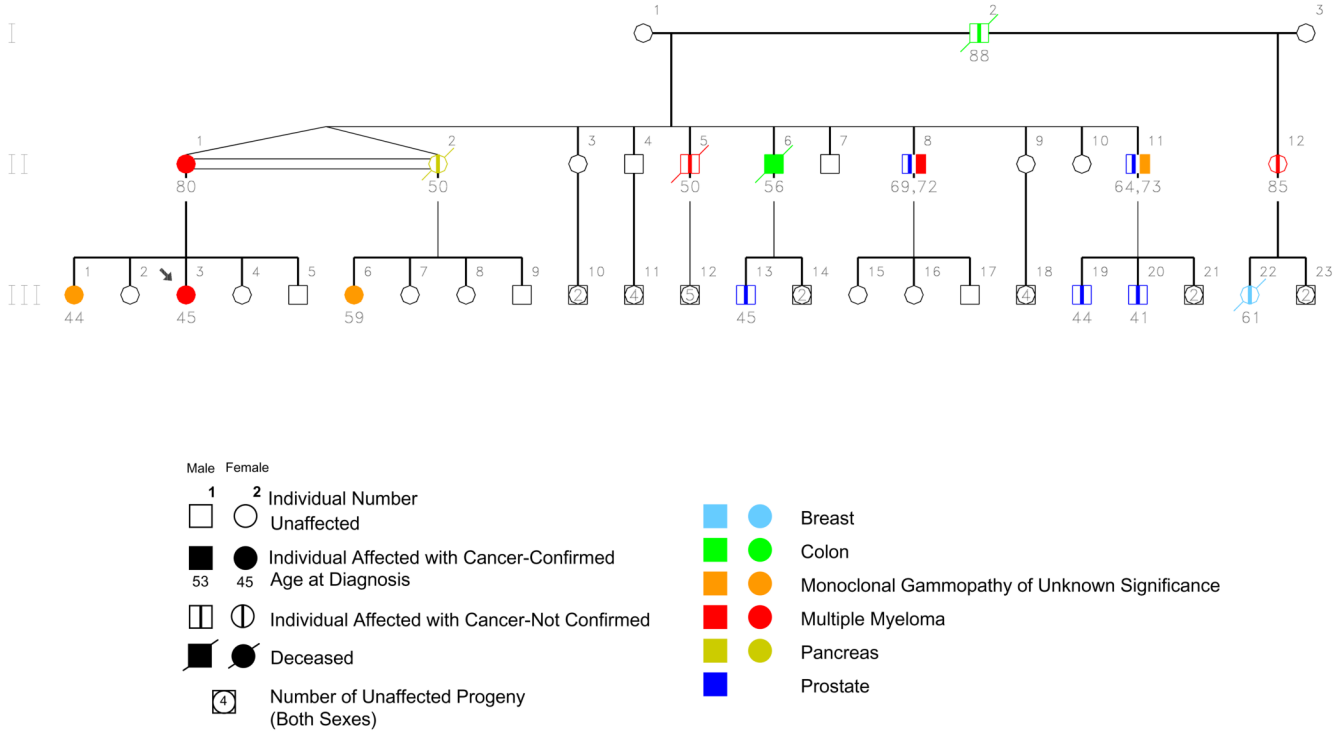

Figure 2.
Pedigree showing multiple family members with myeloma (red), MGUS (orange) in a pattern consistent with autosomal dominant transmission. Note anticipation (earlier disease onset in descendants) and presence of young onset prostate cancer (blue) in this kindred.

Table 1

Serum free light chain results

Patient #	Lambda mg/dL	Kappa mg/dL	Ratio	Monoclonal light chains
III-2	258	505	1.96	-
III-5	207	398	1.92	-
III-1	**296**	**452**	**1.53**	**Lambda**
III-4	238	466	1.96	-
III-6	**165**	**497**	**3.01**	**Kappa**
III-7	282	460	1.63	-
III-8	238	508	2.13	-
II-11	**312**	**147**	**0.47**	**Lambda**
III-17	251	476	1.90	-
III-15	250	587	2.35	-
III-16	309	513	1.66	-

Reference ranges are: Lambda light chains (110–240 mg/dL) Kappa light chains (200–400 mg/dL) Kappa/Lambda ratio (1.35–2.65)