## BRIEF REPORT

# Familial Myeloma

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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 had progeny with two female partners. The progeny had prostate cancer, multiple myeloma, and MGUS.

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MULTIPLE MYELOMA ACCOUNTS FOR APPROXIMATELY 10% OF ALL HEMA-tologic cancers and is most frequent in persons over 65 years of age; only 2% 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 produce a monoclonal protein (M protein) and cause lytic bone lesions. Multiple myeloma can evolve from 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 of most patients with multiple myeloma, and similar changes are also present in MGUS. Persons with MGUS usually have a serum concentration of M protein of less than 30 g per liter and less than 10% bone marrow plasma cells. MGUS 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 blacks than in whites.[7] In a study of 39 families with several cases of multiple myeloma, some family members had MGUS, other types of hematologic cancers, or solid tumors.[8] We report on a black family in which there were five cases of multiple myeloma, three of MGUS, and five of prostate cancer.

### MATERIALS AND METHODS

The study was approved by the institutional review board of Creighton University. Our multiple myeloma–prone family was studied at the University of Arkansas for Medical Sciences and the Creighton University School of Medicine. The methods for developing the family pedigree were the same as those used in our previous study.[8] A detailed genealogic compilation of the family's medical history was obtained with the use of questionnaires and personal interviews that included questions about cancer at all anatomical sites. Individual histories of cancer were confirmed by review of original pathology reports or death certificates whenever possible. Offspring and siblings of myeloma-affected family members were recruited for

evaluation of MGUS, as were 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, as well as four of the authors. During this 1-day meeting, the family was educated about multiple myeloma, with particular emphasis on 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 aid the investigation of the possibility of MGUS.

Serum and urine protein electrophoreses were performed with the Paragon electrophoresis system and an Appraise densitometer (Beckman Coulter) with the use of agarose gel (1.0%) in 1.2% barbital buffer (pH 8.6) on flexible plastic backing. The gels were stained with Paragon blue, consisting of 0.5% (wt/vol) 8-amino-7-(3-nitrophenylazo)-2-(phenylazo)-1-naphthol-3,6-disulfonic acid disodium salt in 5% acetic acid solution (Beckman Coulter). Urine samples were concentrated by a factor of more than 100 with the use of a Minicon concentrator (Millipore). Protein immunofixation electrophoresis on serum or urine was performed with the use of the gels provided with the Paragon electrophoresis system, consisting of 1.0% agarose in a 1.2% TRIS barbital aspartate buffer. The antiserum specimens used were goat IgG fractions against human IgG, IgA, and IgM and the kappa and lambda light chains (Beckman Coulter). After electrophoresis and fixation on the gel, the proteins were stained with Paragon blue. The procedures specified in the manufacturer's instructions were followed after validation in our laboratory.[10] All the tests were performed in the Special Chemistry Laboratory at Creighton Medical Laboratories. Serum kappa and lambda free light chains were measured at ARUP Laboratories by a standard method.[11]

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 on the basis of the observation that the prevalence of MGUS was higher by a factor of three in blacks than in whites in a large series of cases.[7] Because data on prevalence among persons under the age of 50

years are not available, in this study we used rates among persons 50 to 60 years of age for the younger age groups. In Ghana, the prevalence in black men is twice that in white men,[12] which suggests that our expected number is a conservative estimate. On the assumption that the prevalence is lower in younger persons, this approach will overestimate the expected number of cases and thus result in a more conservative statistical test. The observed number was compared with the expected number with the use of Byar's approximation of the Poisson test.[13]

## RESULTS AND DISCUSSION

Table 1 shows the results from 11 first-degree relatives who were evaluated for MGUS with the use of the free light-chain test. In a cohort of this size with this distribution of ages and sexes, less than 1 case of MGUS (0.7 case) would be expected; we found 3 cases (Family Members II-11, III-1, and III-6). M proteins were also found by serum protein electrophoresis patterns in these three family members and were characterized by immunofixation as IgG-λ in Family Members II-11 and III-1 and as IgG-κ in III-6. The serum levels of M proteins in Family Members III-1 and III-6 were too low to be measured. The serum level of M proteins in Family Member II-11 was higher (7.8 g per liter), and the level of the other immunoglobulins

| Table 1. Serum Free Light-Chain Results.* | | | | |
|---|---|---|---|---|
| Family Member | Lambda Light Chains (mg/dl) | Kappa Light Chains (mg/dl) | Kappa:Lambda Ratio | Monoclonal Light Chain Present |
| II-11 | 312 | 147 | 0.47 | IgG-λ |
| III-1 | 296 | 452 | 1.53 | IgG-λ |
| III-2 | 258 | 505 | 1.96 | |
| III-4 | 238 | 466 | 1.96 | |
| III-5 | 207 | 398 | 1.92 | |
| III-6 | 165 | 497 | 3.01 | IgG-κ |
| III-7 | 282 | 460 | 1.63 | |
| III-8 | 238 | 508 | 2.13 | |
| III-15 | 250 | 587 | 2.35 | |
| III-16 | 309 | 513 | 1.66 | |
| III-17 | 251 | 476 | 1.90 | |

* The reference ranges are 110 to 240 mg per deciliter for the lambda light chains, 200 to 400 mg per deciliter for the kappa light chains, and 1.35 to 2.65 for the kappa:lambda ratio.[11]

was reduced (2.4 g per liter). Figure 1 shows the results of assays for serum free light chain. Urine studies of all 11 family members tested yielded no evidence of M proteins or monoclonal free light chains.

The pedigree (Fig. 2) shows the five family members with multiple myeloma and the three with MGUS. Family Member I-2 is the putative progenitor. He died of colon cancer at the age of 88 years. Multiple myeloma developed in his progeny from two women: in II-12, his daughter from his first partner, and in II-1, II-5, and II-8, his children from his second partner. In the third generation, the proband (III-3) had multiple myeloma, and two other family members had MGUS. All these persons were in the direct line of descent from the putative progenitor. Family Member II-2 died at the age of 50 years of pancreatic cancer, and her identical twin (II-1) had multiple myeloma. The daughter of II-2 (III-6) has MGUS. Family Member II-8 was found to have prostate cancer at the age of 69 years and multiple myeloma at the age of 72 years. That man's brother, II-11, had prostate cancer at 64 years of age and MGUS at 73 years of age. Family Member II-11 has two sons, III-19 and III-20, who received a diagnosis of prostate cancer at 44 and 41 years of age, respectively.

We previously reported another family that included a sibship of seven, of whom three had multiple myeloma and two had MGUS.[14] One sibling had two primary cancers (prostate cancer and multiple myeloma), and systemic amyloidosis developed in one sibling who had MGUS; the father of this sibship also had prostate cancer.[8] These observations led us to investigate additional instances of familial multiple myeloma.[8]

The overall risk of multiple myeloma in first-degree relatives of persons with multiple myeloma is reported to be increased by a factor of two to four.[15] The risk of hematologic and solid cancers, especially chronic lymphocytic leukemia, non-Hodgkin's lymphoma,[4] prostate cancer, and endometrial cancer,[8,14,16,17] also appears to be higher in relatives of persons with multiple myeloma.[8] Brown et al.[18] reported an increased risk of multiple myeloma associated with a family history of any hematologic cancer (odds ratio, 1.7) but did not find a significant increase in the rate of solid cancers in white or black families in the

**Figure 1 (facing page). New Cases of Monoclonal Gammopathy of Undetermined Significance (MGUS) in Clinically Unaffected Family Members II-11 (Panel A), III-1 (Panel B), and III-6 (Panel C), Documented by Serum Protein Electrophoresis (SPE) and Serum Immunofixation.**
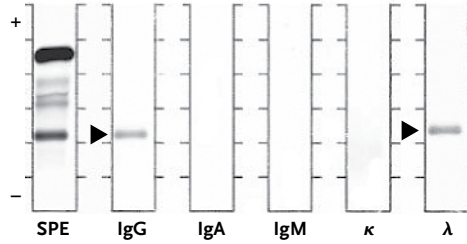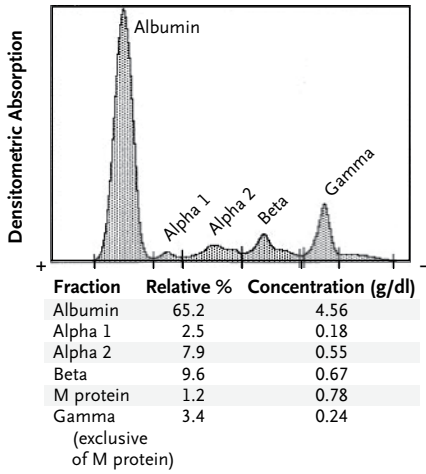
The cases were detected as a result of investigation by the study's family information service. The graphs on the left side of each panel show densitometric tracings of the total serum proteins. Albumin is the largest single-protein peak; the alpha 1, alpha 2, beta, and gamma peaks contain multiple globulins. Small peaks in the gamma fraction indicate the presence of M proteins (a single immunoglobulin produced in excessive quantities from a single plasma-cell clone). In a normal electrophoretic pattern, the gamma fraction is broad because of the polyclonal nature of the many different immunoglobulins produced by many different plasma cells. An abnormal electrophoretic pattern has a tall, narrow peak indicating the presence of an M protein. The columns on the right side of each panel depict immunofixation of serum proteins on agarose gels. The first column shows all serum proteins, and the other columns show specific immunoglobulin subtypes (IgG, IgA, IgM, and kappa and lambda light chains), as identified by immunofixation to specific antiserum. The bands indicate subtypes of monoclonal proteins (M proteins). The arrowheads indicate the presence of monoclonal proteins, as detected in the densitometric tracing, that are identified by immunofixation. Plus and minus signs indicate the positions of the positive and negative electrodes.

United States. Eriksson and Hallberg,[16] however, in a smaller study of Swedish families with various cancers, identified an increased risk of prostate cancer in first-degree relatives of persons with multiple myeloma (relative risk, 3.11).[16]
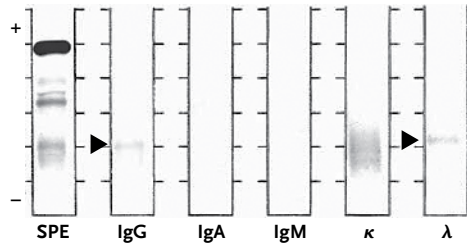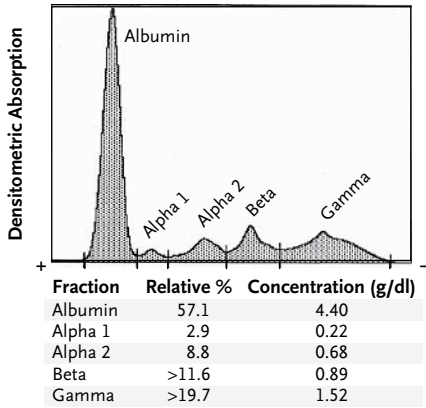
Evidence of an increased risk of multiple myeloma in relatives of carriers of the *BRCA1* or *BRCA2* mutation has also been reported.[19] In addition, Dilworth et al.[20] described a melanoma-prone family in which one member with multiple myeloma had a germ-line mutation of the *CDKN2A* (*p16*) gene. To determine whether the *CDKN2A* mutation was responsible for multiple myeloma, these investigators searched for loss of heterozygosity and found that the wild-type *CDKN2A* allele was lost in the malignant plasma cells, a result suggesting that germ-line mutations of *CDKN2A* may confer an increased susceptibility to multiple myeloma as well as to melanoma and pancreatic cancer.[21]

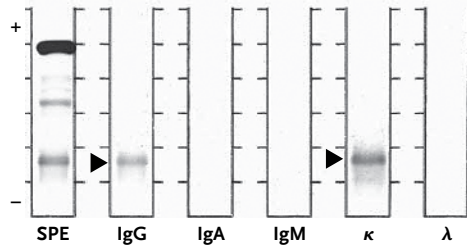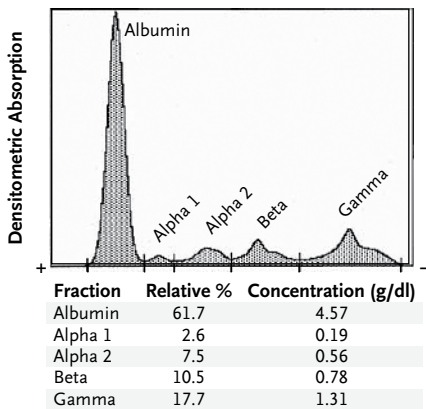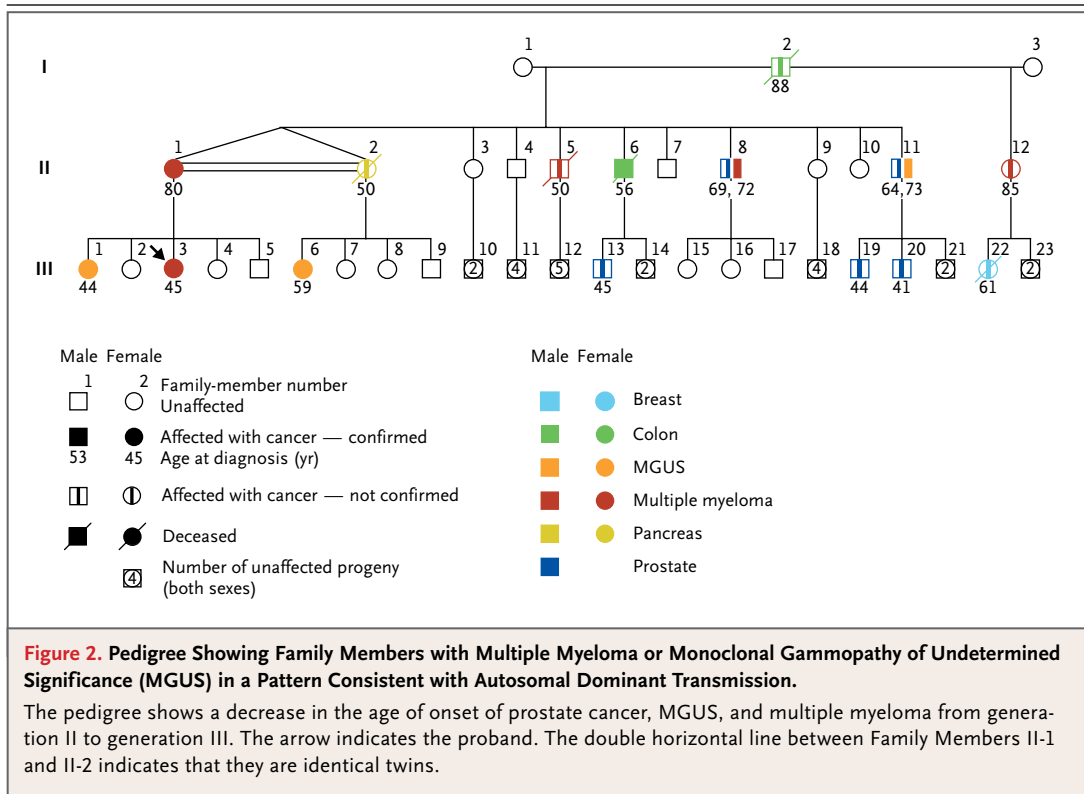In conclusion, this myeloma-prone family mer-

**A Patient II-11**



| Fraction | Relative % | Concentration (g/dl) |
|---|---|---|
| Albumin | 65.2 | 4.56 |
| Alpha 1 | 2.5 | 0.18 |
| Alpha 2 | 7.9 | 0.55 |
| Beta | 9.6 | 0.67 |
| M protein | 1.2 | 0.78 |
| Gamma (exclusive of M protein) | 3.4 | 0.24 |

**B Patient III-1**



| Fraction | Relative % | Concentration (g/dl) |
|---|---|---|
| Albumin | 57.1 | 4.40 |
| Alpha 1 | 2.9 | 0.22 |
| Alpha 2 | 8.8 | 0.68 |
| Beta | >11.6 | 0.89 |
| Gamma | >19.7 | 1.52 |

**C Patient III-6**



| Fraction | Relative % | Concentration (g/dl) |
|---|---|---|
| Albumin | 61.7 | 4.57 |
| Alpha 1 | 2.6 | 0.19 |
| Alpha 2 | 7.5 | 0.56 |
| Beta | 10.5 | 0.78 |
| Gamma | 17.7 | 1.31 |

**Figure 2. Pedigree Showing Family Members with Multiple Myeloma or Monoclonal Gammopathy of Undetermined Significance (MGUS) in a Pattern Consistent with Autosomal Dominant Transmission.**

The pedigree shows a decrease in the age of onset of prostate cancer, MGUS, and multiple myeloma from generation II to generation III. The arrow indicates the proband. The double horizontal line between Family Members II-1 and II-2 indicates that they are identical twins.

its long-term medical and genetic follow-up, including formal linkage analysis, in search of a cancer-susceptibility locus.

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