CORRESPONDENCE

Re: Familial Multiple Myeloma: a Family Study and Review of the Literature

Multiple myeloma (MM) is one of the hematologic malignancies with the poorest outlook. Although very little is known about the causes and the molecular defects underlying MM development, the identification of familial clusters of MM has suggested possible involvement of genetic factors. In this respect, Lynch et al. (1) have reported on a family in which three siblings have MM. Although such families are rare, they represent a precious resource for identifying the genes that predispose individuals to MM and potential targets for new therapeutic strategies.

We report on a family in which four members in three generations are affected with MM (Fig. 1). Three of the cases were diagnosed at an early age (two at age 56 years and one at age 65 years). Taking into account both the distribution of MM within this family and the prevalence of this rare disorder within the general population (3.1 cases/100,000 individuals per year in France) (2), as well as the age at cancer onset in this kindred, it is very likely that a genetic factor could explain the present familial clustering. The occurrence of MM within this family is compatible with an autosomal dominant mode of inheritance, incomplete penetrance, and possible anticipation. It is interesting that, in our kindred, all cases have arisen in women, two of whom have also developed breast cancer. Germline mutations in BRCA1 and BRCA2 increase considerably the risk of breast cancer (3) as well as other malignancies, and families with hematologic malignancies in BRCA1/2 mutation carriers have been reported (4). Using previously published methods (5), we therefore analyzed the relationship between BRCA1/2 mutations and the appearance of MM by searching for germline mutations in the proband of this family, who was diagnosed with an immunoglobulin A lambda (IgA\(\lambda\)) MM at age 56 years.

We detected no deleterious mutation or polymorphism of BRCA1 in the proband. In contrast, we found that the proband carried a nonsense mutation, A10204T, in exon 27 of BRCA2 that corresponds to a Lys 3326 Stop substitution predicted to cause loss of the final 93 amino acids of the BRCA2 protein. Variations in the BRCA1 and BRCA2 coding sequences that lead to a truncated protein are usually considered disease-associated mutations. However, because this particular variation has been observed both in cancer patients and in control subjects, its biologic consequence remains unclear (6,7). We also identified a variation of the noncoding intronic sequence of BRCA2, corresponding to a substitution 16 nucleotides upstream of exon 25 (IVS25–16 T/C).

The absence of a proven deleterious BRCA1 or BRCA2 mutation in the proband, even though a genetic predisposition to MM is almost certain, may have at least three explanations. First, current genetic testing methods lack sufficient sensitivity to allow the identification of all existing mutations, particularly large genetic alterations. Second, the BRCA2 nonsense mutation A10204T might play a role in the development of the MM phenotype, either as a reduced penetrance disease mutation or as a cofactor (i.e., modifier gene). Third, other dominant genes could be involved in the MM predisposition. In the absence of segregation analysis, the mode of inheritance of MM remains poorly understood. In our kindred, only women were affected with MM, an unexpected finding given the 50% sex ratio in the general population (2) and the case of autosomal dominant mode of inheritance of MM reported by Lynch et al. (1). In addition, the genetic defect that predisposes individuals to MM seems also to be transmitted through apparently unaffected female family members. Consequently, we cannot exclude a dominant X-linked mode of inheritance, with inviability in male gene carriers.

Because families with more than two cases of MM are extremely rare, the present observation, supporting a genetic basis for at least a fraction of cases, represents an important contribution to a better understanding of the pathogenesis of this disease, which is usually associated with a fatal outcome.

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REFERENCES

(1) Lynch HT, Sanger WG, Pirruccello S, Quinn-Laquer B, Weisenburger DD. Familial multiple myeloma: a family study and review of

Fig. 1. Pedigree of a family with multiple myeloma. Solid circles represent females with cancer; open circles and open squares represent unaffected females and males, respectively. Diagonal lines indicate deceased individuals, and the arrow indicates the proband. The roman numbers in the left margin refer to generation numbers. MM = multiple myeloma; D = deceased; y = year; number in parenthesis = age at onset, current age, or age of death.


**NOTES**

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