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RESEARCH ARTICLE

Clinical characteristics and outcome of 318 families with familial monoclonal gammopathy: A multicenter Intergroupe Francophone du Myélome study

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Abstract

Familial forms of monoclonal gammopathy, defined as multiple myeloma (MM) or Monoclonal Gammopathy of Undetermined Significance (MGUS), are relatively infrequent and most series reported in the literature describe a limited number of families. MM rarely occurs in a familial context. MGUS is observed much more commonly, which can in some cases evolve toward full-blown MM. Although recurrent cytogenetic abnormalities have been described in tumor cells of sporadic cases of MM, the pathogenesis of familial MM remains largely unexplained. In order to identify genetic factors predisposing to familial monoclonal gammopathy, the Intergroupe Francophone du Myélome identified 318 families with at least two confirmed cases of monoclonal gammopathy. There were 169 families with parent/child pairs and 164 families with cases in at least two siblings, compatible with an autosomal transmission. These familial cases were compared with sporadic cases who were matched for age at diagnosis, sex and immunoglobulin isotype, with 10 sporadic cases for each

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familial case. The gender distribution, age and immunoglobulin subtypes of familial cases were unremarkable in comparison to sporadic cases. With a median follow-up of 7.4 years after diagnosis, the percentage of MGUS cases having evolved to MM was 3%. The median overall survival of the 148 familial MM cases was longer than that of matched sporadic cases, with projected values of 7.6 and 16.1 years in patients older and younger than 65 years, respectively. These data suggest that familial cases of monoclonal gammopathy are similar to sporadic cases in terms of clinical presentation and carry a better prognosis.

1 | INTRODUCTION

Multiple myeloma (MM) is the second most frequent hematological malignancy after lymphoma, with an estimated annual incidence of 4–6/100000 in the United States.[1] Occurrence of monoclonal gammopathy of undetermined significance (MGUS) is much more frequent, with an increasing incidence in elderly individuals. It has been estimated that up to 2% of patients older than 50 years have a detectable monoclonal component in their serum, with an estimated global risk of evolution to full-blown myeloma of 1% per year.[1] With a median age at diagnosis of 65 years in several series, the normalized incidence was found to be higher in males (sex ratio of 1.5). In a national hospital-based series, we recently reported that the median age at diagnosis in France was 72 years in males and 76 years in females.[2]

Familial predisposition is considered less frequent in the case of MM in comparison to other hematological malignancies. Kindreds of patients with chronic lymphocytic leukemia (CLL) have an increased risk of bearing clonal B cells. In the case of acute leukemia, there is an increased risk of disease up to three- to five-fold in first- and second-degree relatives. First-degree relatives of patients with Waldenström's disease (WM) have a 20-fold increased risk of developing this disease.[3] In a study pooling 11 case–control studies, Schinasi et al. found that the risk of MM was elevated in association with having a first-degree relative with any lymphoproliferative disorder but was more pronounced (OR = 1.90) in patients with a first-degree relative with MM.[4] Clay-Gilmour et al. reported an increased risk of monoclonal gammopathy in first-degree relatives of patients with MM or MGUS, with a 2.4-fold higher prevalence than expected.[5] Kristinsson et al. estimated that first-degree relatives of patients with MM had a 2.1 increased risk of developing MM or MGUS.[6] In a large retrospective analysis of patients with plasma cell disorder, defined as MM, MGUS or AL amyloidosis, Visram et al. found that 2.7% of patients reported having a family member with plasma cell disorder.[7] These results suggest a shared genetic susceptibility to MM and MGUS, as supported by the fact that the MM polygenic risk score is also associated with the occurrence of MGUS.[8]

To better understand the prevalence and the characteristics of familial monoclonal gammopathy, we initiated a nationwide study of families with at least two cases of monoclonal gammopathy, defined as confirmed myeloma or MGUS (NCT02853214). This ongoing study has presently allowed us to identify 318 families with 837 afflicted family members (median number of 2.5 cases per family, range 2–9). A biological database has been constituted including peripheral blood cells, serum and establishment of lymphoblastoid cell lines (success rate 92%). This biological resource has allowed us to initiate the identification of candidate genes of predisposition to familial monoclonal gammopathy, with the demonstration that mutations in *DIS3* are likely to be involved in a small number of families.[9] In the present report, we present a description of the clinical characteristics of this cohort, including relationships between affected family members, disease characteristics and outcome.

2 | PATIENTS AND METHODS

Families with MM were identified in the context of a national prospective program initiated in France in 2007 (PHRC national INCA). Forty-seven centers from the Intergroupe Francophone du Myélome (IFM) participated in the recruitment of index cases. Healthy family members and members with unknown disease status were then solicited. Patients with unknown status underwent serum electrophoresis and immunoelectrophoresis to determine their status. All persons provided signed informed consent and the protocol was approved by the Comité de Protection des Personnes Sud Est IV. While the collection of new cases is still ongoing, the present study contains data on families identified between 2008 and 2019. For survival studies, the 148 patients with familial MM were compared with 1480 case-matched sporadic cases, chosen among a large database constituted by patients included in IFM trials. Sporadic cases were matched for sex, age at diagnosis and immunoglobulin subtype.

Since the primary aim of this project was the identification and characterization of genetic variants predisposing to monoclonal gammopathy in families with at least two cases (defined as myeloma and MGUS) with biological sampling (serum and peripheral blood cells in order to establish lymphoblastoid cell lines), clinical information was gathered retrospectively in a selected subgroup of families, and we did not have access to additional patient characteristics. MGUS was defined by the presence of a quantifiable monoclonal component in serum.

3 | STATISTICS

Descriptive analyses were performed to summarize the characteristics of the MGUS and MM cases (demographics and familial relationships,

monoclonal component, follow-up duration and vital status). Median, minimum and maximum values were computed for quantitative variables, and count and frequency for qualitative ones. In order to determine whether the prognosis of familial cases of MM was different from that of sporadic cases of myeloma, our familial cohort was compared with a large Intergroupe Francophone du Myélome (IFM) cohort of sporadic cases. All statistical analyses were performed using R software, version 4.0.2.[10] To account for potential imbalance in the distribution of the individual's characteristics between the familial and sporadic cohorts, a propensity score matching was performed. The familial 'cases' consisted of 148 individuals with complete data and mainly IgG or IgA heavy chain. The sporadic 'controls' consisted of 6364 individuals with sporadic MM cases with complete data, either IgG or IgA heavy chain, and with age at diagnosis ranging from 35 to 90 years. The propensity score (PS) corresponded to the probability of belonging to familial cases given the value of baseline characteristics. This score was estimated for each familial or sporadic individual, from a penalized, generalized additive model (GAM), using *mgcv* package.[11] The logit of the PS was modeled as a function of sex, type of heavy chain, a sex-heavy chain interaction, a penalized spline of age, a penalized spline of the year of diagnosis, an interaction term of age multiplied by a penalized spline of the year of diagnosis, two penalized splines of age modeling the difference of the effect of age between female and male (the reference), and between IgA and IgG (the reference) heavy chain subtype. The splines of age and year were restricted cubic splines with 7 knots (age: based on the quantiles of age; year: evenly spaced between 2000 and 2019). The number of sporadic controls was much larger than that of familial cases, so each familial case was matched to 10 controls without replacement. Greedy matching was performed using calipers of width equal to 0.2 of the standard deviation of the logit of the PS, using the *Matching* package.[12,13] Following the recommendations made by Austin, the balance of the distribution of the individuals' characteristics, between the two cohorts, was assessed before and after matching in three ways.[14] First, absolute standardized differences, defined as |mean in cases−mean in controls|/standard deviation in cases, were computed to compare means or prevalence between the two cohorts. Second, variances were compared, using the ratio of the variance in cases divided by the weighted variance in controls. Third, quantile–quantile plots for age at diagnosis and year of diagnosis were drawn (overall, and by different stratifying variables). After matching, the survival was estimated using the Kaplan–Meier method, and absolute differences in survival between the matched cases and controls were computed using the Kaplan–Meier estimates. The survival curve for familial cases and sporadic controls were compared using a log-rank test that was stratified on the matching 11 uplets, this log-rank test was performed using the *coin* package.[15,16] Percentile-based confidence intervals were computed based on 10 000 bootstrap samples. Each bootstrap sample was obtained by randomly sampling, with replacement, 148 matching uplets, to account for the dependency of the observations induced by the matching process. Median survival time for a given cohort was estimated by inverting the Kaplan–Meier survival curve.

4 | RESULTS AND DISCUSSION

There are relatively few reports in the literature on familial cases of myeloma. Grosbois et al. reported 15 families.[17] In a review of the literature published in 1995, Crozes-Bony et al. identified 52 previously reported cases of familial myeloma.[18] In a review of the literature, Roddie et al. identified 53 families.[19] Eriksson reported that the risk of being diagnosed with MM was increased 5.6-fold in individuals who had a relative with MM.[20] In a large Swedish registry-based study, Altieri et al. found that MM cases tended to be clustered along with cases of CLL and NHL, with a standardized incidence ratio of 2.45.[21]

Over a 11-year period and thanks to the contribution of the AF3M patient advocacy group and the Intergroupe Francophone du Myélome (IFM) clinical trials group, a total of 318 families with at least two confirmed cases of monoclonal gammopathy were identified in France (Figure S1), including 265 individuals with MGUS and 241 patients with MM. As summarized in Table 1, these included 147 families with at least two cases of myeloma, 88 families with at least two cases of MGUS and 116 families with 1 case of MGUS and 1 case of MM. Additionally, this study identified 13 cases with amyloidosis (including 8 amyloidosis cases, 4 cases MM/amyloidosis and 1 case Waldenström/amyloidosis) and 55 cases with Waldenström's disease.

Familial relationships between affected individuals in 318 families are summarized in Table 1. One hundred seventy-five families had at least one parent and one child with monoclonal gammopathy, and 169 families had at least two siblings concerned. Altieri et al. suggested that the pattern of familial MM observed in the Swedish registry was consistent with an autosomal dominant mode of inheritance, in concordance with our observations.[21] In our families, there were slightly more females with MGUS (54%) and more males with confirmed MM (52%).

Age at diagnosis of MGUS and MM was similar (65.3 and 64.4 years, respectively) in our familial series. Halvarsson et al. found a similar age at diagnosis for familial and sporadic cases of myeloma (66.0 vs. 68.4 years).[22] In a report on eight African American families with familial MM, Jain et al. reported a median age at diagnosis of myeloma of 61 years.[23] In our series, there were 175 cases of parent/child pairs. In families with afflicted parents and children, the median ages at diagnosis for MM and MGUS in parents were respectively 73.5 years (80.5 years in males and 72.5 years in females) and 81 years (79.5 years in males and 84 years in females), while the median ages in children were 56 years (55.5 years in males and 56 years in females) and 58 years (56 years in males and 60 years in females). Our observations were thus consistent with a study from Deshpande et al. who observed that the onset of plasma cell dyscrasias tended to occur at a younger age in second-generation cases (50 vs. 71 years).[24]

Data were available concerning the type of monoclonal component for 453 index cases (208 MM and 245 MGUS) with a majority of IgG components (69% of MM cases and 59% of MGUS cases). The light chain component was kappa in 70% of all MM cases and in 59% of all MGUS cases. Fourteen percent of all MM cases were light chain

TABLE 1 Familial relationships of index cases in 318 families with at least two cases of monoclonal gammopathy

	All families	≥2 cases MM	≥2 cases MGUS	Other (1 MM + 1 MGUS)	>1 case WM + other	>2 cases WM	Amyloidosis and 1 case MM/MGUS
Parent/child	175	63	27	48	16	15	6
Siblings	169	50	41	47	14	12	5
Cousins/uncles	31	14	6	8	1	2	0
Other	54	20	14	13	4	2	1
Total		147	88	116	35	31	12

TABLE 2 Diseases associated with familial monoclonal gammopathy

Disease	MM	MGUS	Other family members
Neoplasia			
Prostate cancer	2	1	1
Pheochromocytoma	1	0	0
Pancreatic cancer	0	0	5
Ovarian cancer	0	0	1
Breast cancer	3	2	6
Bladder cancer	0	1	1
Lung cancer	0	1	2
Stomach cancer	0	0	2
Colorectal cancer	1	1	2
Melanoma	1	0	0
Esophageal cancer	0	0	1
Mesothelioma	0	0	2
Uterine cancer	0	0	1
NHL	1	0	1
PV	0	1	0
CLL	1	0	1
AML	0	0	2
MDS	2	0	0
Autoimmune/inflammatory disease			
Basedow	1	0	0
Crohn's disease	0	0	1
RA	0	2	0
DLE	1	0	0

Abbreviations: AML, acute myeloid leukemia; CLL, chronic lymphocytic leukemia; DLE, diffuse lupus erythematosus; MDS, myelodysplastic syndrome; NHL, non-Hodgkin's lymphoma; PV, polycythemia vera; RA, rheumatoid arthritis.

disease. Only two exclusively light chain components were identified among MGUS cases, but this is probably an underestimation since not all patients underwent urine analyses or determination of serum-free light chains. Twenty-six percent of MGUS cases were IgM components. Overall, the characteristics of the monoclonal components in familial cases were unremarkable in comparison to sporadic cases.

Associated diseases were observed in patients with familial gammopathy and are listed in Table 2. Nonhematological cancers were identified in 8 cases of patients with MM, 6 cases of patients with MGUS and 24 other family members. These data do not show any evidence of increased risk of associated neoplasia but are likely to be underestimated as they were obtained by declaration of one of the family members. Altieri et al. identified associations between familial cases of myeloma and rectal, stomach, cervical, prostate, bladder, endocrine glands and connective tissue malignancies.[21] Frank et al. reported that sporadic cases of MM were reliably associated with the presence in a first-degree relative of colorectal, breast and prostate cancers, nonthyroid endocrine tumors, leukemia and cancer of unknown primary.[25] Grufferman et al. performed a study of family history of central nervous system diseases in a case–control study of

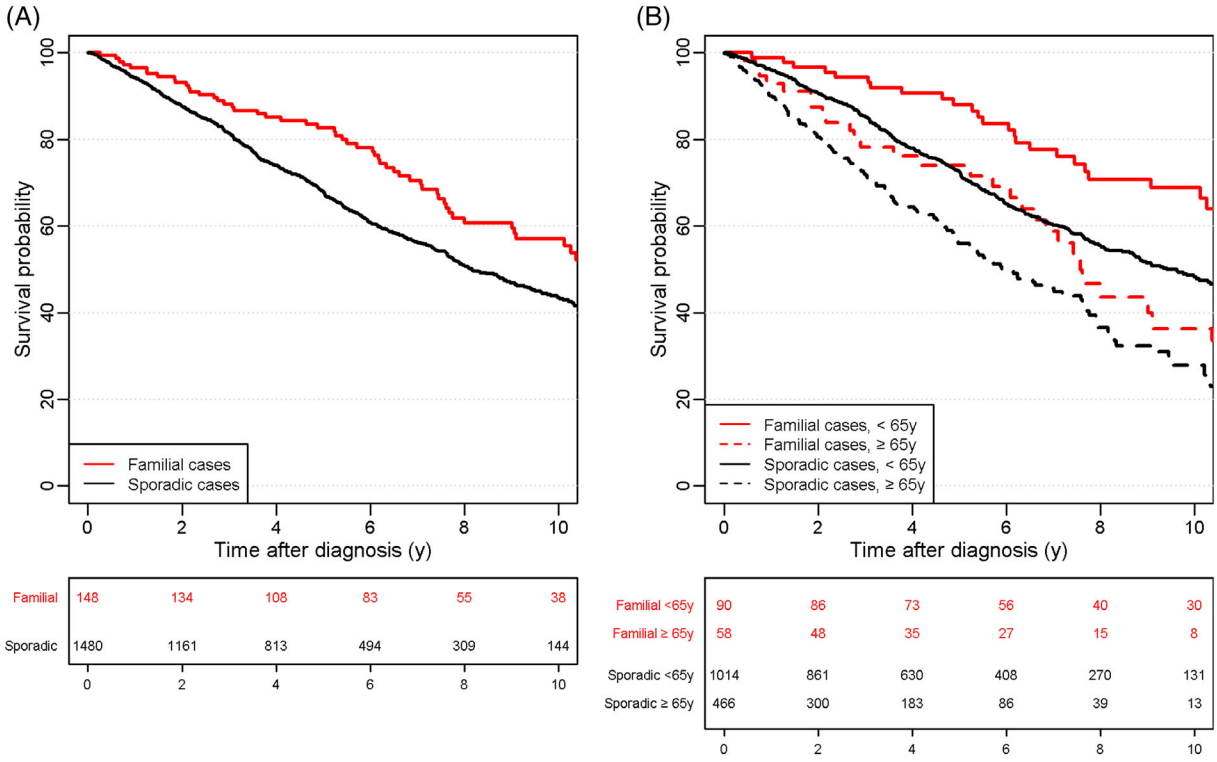

FIGURE 1 Overall survival curves of the 148 patients with familial forms of multiple myeloma (MM) and the 1480 case-matched sporadic controls with MM. (A) All patients, (B) according to age. [Color figure can be viewed at wileyonlinelibrary.com]

sporadic MM and observed a 4.4 relative risk of degenerative or demyelinating central nervous system disease in first-degree relatives of myeloma patients.[26] Lynch et al. reported a family with five cases of MM, three cases of monoclonal gammopathy of undetermined significance (MGUS) and five cases of prostate cancer in two generations.[27] Chang et al. reported an increased risk of follicular lymphoma in patients with familial myeloma.[28]

With a median follow-up of 7.42 years since diagnosis, 14 of the 265 MGUS patients (5.3%) evolved from MGUS status to a confirmed diagnosis of hematological malignancy with 8 cases of MM (3%), 4 cases of NHL, 1 case of WM and 1 case of amyloidosis. The median age of MGUS patients who evolved was 62 years (range 45–87 years). Visram et al. reported a higher risk of progression to a plasma cell or a lymphoproliferative disorder in familial versus nonfamilial MGUS cases in spite of a 50% lower risk of death in familial MGUS patients. During follow-up, 23 patients (9.7%) of the patients in our series with MGUS died, including 12 who died at an age greater than 85. With a median follow-up of 6 years after diagnosis, 91 patients of the 241 MM patients (37.8%) had died, including 80 who died as a result of their disease. The results from the survival analyses that are presented hereafter were obtained using the data obtained from the 148 familial cases of MM and from the 1480 case-matched sporadic controls of MM (characteristics provided in Table S1). Overall survival time was found to be longer in the 148 familial MM cases than in the 1480 cased-matched sporadic MM cases (Figure 1A, $p = .0017$). Median survival times were 11.3 and 8.2 years and 5-year survivals (95% confidence interval) were 82.6% (76.0%–88.7%) and 68% (65.2%–70.5%), for familial and sporadic MM cases, respectively. In patients aged under 65 years at diagnosis (Figure 1B), median survival times were 16.1 and 9.4 years and 5-year survivals were 88.0% (80.3%–94.7%) and 72.6% (69.8%–75.3%), respectively. In MM patients aged 65 years and over, median survival times were 7.6 and 5.9 years and 5-year survivals were 73.9% (61.6%–85.7%) and 56% (50%–61.4%), respectively. Differences in 5-year survival familial versus sporadic MM cases were +15.3% (+7.5%–22.4%) for patients aged under 65 years and +18.0% (+5.7%–30.4%) for patients aged 65 years and over, showing that 5-year survival was greater for the familial MM cases than for the sporadic ones, whatever the age class. Overall, these data suggest that familial cases of MM are similar to sporadic cases in terms of age of onset with a better prognosis than sporadic cases. This result is in contrast to those reported in Waldenström's macroglobulinemia in which familial forms have been reported to carry a worse prognosis than sporadic forms[29] but is in keeping with the observation reported by Visram et al.[7] In solid tumors, the impact of a familial versus a sporadic form appears to be highly dependent on the tumor type.[30–32]

Familial predisposition to monoclonal gammopathy remains largely unexplained. Grass et al. studied the status of Paratarg-7, a target for monoclonal proteins in various types of lymphoid malignancies.[33] They found that paraproteins of affected members with familial MGUS/MM share family-typical hyperphosphorylated antigens. Halvarsson et al. analyzed 38 familial cases of myeloma for known sporadic MM risk alleles and observed risk alleles at CCAT1, suggesting a polygenic etiology for these familial cases.[22] Genetic

predisposition to myeloma has been studied using GWAS approaches. Performing a meta-analysis of two GWAS studies, Morgan et al. identified SNPs robustly associated with MM risk.[34] Analysis of these SNPs in patients with MGUS showed that each SNP independently increased the risk of occurrence of MGUS, suggesting that MGUS occurrence is likely to be polygenic.[35] Went et al. identified 24 risk variants estimated to explain 16% of heritability of MM.[36] Clay-Gilmour et al. found that the 23 gene polygenic risk score developed for MM was similarly associated with MGUS, independently of age, sex or immunoglobulin isotype.[8] Using a GWAS approach Li et al. observed that a genetic variation at 5q15 was associated with an increased hereditary risk of MM and suggested that this could be linked to a reduced expression of ELL2, a critical factor involved in B cell differentiation, associated with increased ribosomal gene expression.[37,38] Collectively variants identified by GWAS explain approximately 15% of familial risk.[39,40] We have recently shown that germline variants of Dis3, a gene previously found to be somatically mutated in approximately 12% cases of sporadic myeloma,[41] were identified in 2.6% of families with multiple cases of monoclonal gammopathy.[9] Additionally, familial cases may be due to exposure to common causative agents in the environment. In the case of myeloma, extensive analyses of environmental toxins have not conclusively shown the role of vinyl chloride,[42] dioxin,[43] diesel,[44] alachlor[45] and benzene.[46] In our series, we did not have access to data regarding potential environmental factors.

Familial monoclonal gammopathy represents a small minority of all cases of monoclonal gammopathy. While our study was not designed to exhaustively identify all cases in France over the study period, the participation of a large majority of treatment centers thanks to the IFM group has identified an approximate number of 30 new families with monoclonal gammopathy each year, to be compared with over 6000 new cases of MM overall. Our results suggest that the biological and clinical characteristics of familial cases are similar to those of sporadic cases and in particular that the evolution and prognosis of familial cases are more favorable than that of sporadic cases. Importantly, this is in keeping with a similar observation recently published by Visram et al., showing that a familial history of plasma cell disorders was associated with improved survival in patients with MGUS, MM and systemic AL amyloidosis.[7] In this large retrospective analysis, the crude hazard ratio for overall survival was 0.52 (95% CI 0.40–0.67) with a median survival for familial MM patients of 9.2 years as compared with 5.8 years in non-familial cases. Currently available data provide possible genetic predisposition hypotheses for a minority of all familial cases and additional collaborative studies on large cohorts are required to better understand the determinants of this disease.

AUTHOR CONTRIBUTIONS

All authors have read and approved this manuscript.

Charles Dumontet participated in the design of the study, data analysis, obtaining funding and writing the manuscript. Delphine Demangel, Perrine Massot and Emeline Perrial participated in patient accrual, obtaining and processing clinical data. Lionel Karlin, Camille Golfier, Marie-Charlotte Laudé, Xavier Leleu, Philippe Rodon, Murielle Roussel, Isabelle Azaïs, Chantal Doyen, Borhane Slama, Salomon Manier, Olivier Decaux, Marie Beaumont, Denis Caillot, Manuel Cliquennois, Pascale Cony-Makhoul, Anne-Violaine Doncker, Véronique Dorvaux, Jean Fontan, Bénédicte Hivert, Isabelle Leduc, Cécile Leyronnas, Margaret Macro, Michel Maigre, Clara Mariette, Philippe Mineur, Sophie Rigaudeau, Bruno Royer and Laure Vincent participated in patient accrual. Laurent Roche and Mathieu Fauvernier performed the case–control analysis. Maroulio Pertesi, James Mckay and Laurent Garderet participated in the design of the study, data analysis and writing of the manuscript.

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CONFLICT OF INTEREST

None of the authors have any disclosures.

DATA AVAILABILITY STATEMENT

Data available on request due to privacy/ethical restrictions

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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