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Familial lymphoid neoplasms in patients with mantle cell lymphoma

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A B S T R A C T

Background and Objectives. Familial aggregation has been recognized in patients with several lymphoid neoplasms, but the genetic basis for this familial clustering is not known. Germ-line mutations in the ataxia-telangiectasia mutated (*ATM*) and *CHK2* genes have been detected in patients with mantle cell lymphoma (MCL), suggesting a potential role of these genes in genetic predisposition to these tumors. However, no familial association has been previously recognized in MCL.

Design and Methods. To determine the possible existence of familial lymphoid neoplasms in MCL, we searched clinical records of MCL patients and identified three families in which a MCL, an acute B-cell lymphoblastic leukemia, and a lymphoplasmacytic lymphoma occurred in a first-degree relative of a MCL patient.

Results. The neoplasms in two daughters appeared at an earlier age and were more aggressive than that in the respective parent, suggesting that the phenomenon of anticipation may characterize familial lymphomas associated with MCL. No mutations were detected in the *ATM*, *CHK2*, *CHK1*, and *p53* genes.

Interpretation and Conclusions. Our findings suggest that inactivation of the investigated DNA damage response genes do not account for familial disease aggregation in MCL patients, although such aggregation may occur and seems to be associated with the phenomenon of anticipation.

Key words: mantle cell lymphoma, *ATM*, *CHK2*, *CHK1*, *p53*.

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Mantle cell lymphoma (MCL) is a malignant lymphoproliferative disorder genetically characterized by the t(11;14)(q13;q32) translocation, which leads to the rearrangement and overexpression of the cyclin D1 gene.[1,2] This neoplasm accounts for 2.5-10% of all cases of non-Hodgkin's lymphoma (NHL) and appears more frequently in elderly males. The clinical evolution of MCL is aggressive with a median overall survival of only 3 to 4 years, and with a low percentage of cases with total remission.

Clinical and epidemiological studies have identified familial aggregation of some lymphoid neoplasms, suggesting a potential role for inherited factors in the development of these disorders. Familial clusters of neoplasms have been described in chronic lymphocytic leukemia (CLL), follicular lymphoma (FL), multiple myeloma (MM), and Hodgkin's disease (HD).[3-10] However, familial aggregation in MCL patients has not been previously recognized. Studies of familial CLL have shown vertical transmission of the disease and other lymphoid neoplasms, suggesting that this predisposition may be caused by a inherited genetic factor with incomplete penetrance and a pleiotropic effect.[3,9] However, the molecular and genetic bases of these familial aggregations remain elusive. One of the most common genetic alterations in CLL and MCL is the 11q23 deletion, frequently associated with mutations of the ataxia-telangiectasia mutated (ATM) gene.[11,12] The *ATM* gene plays a central role in DNA damage response pathways and its inactivation has been associated with increased chromosomal instability.[13,14] Ataxia-telangiectasia (A-T) patients have an increased risk of lymphoid neoplasms and A-T carriers may have a higher susceptibility to cancer.[15] *ATM* gene mutations have been identified in the germ-line of some CLL and MCL patients, raising the question of whether

this gene may also play a role in the genetic predisposition to this lymphoma.[16-18] *CHK1*, *CHK2* and *p53* are *ATM* down stream genes also involved in the DNA damage response pathway that participates in the pathogenesis of different human tumors and hereditary cancer neoplasms.[19,20] Particularly, *CHK2* germ line mutations have been reported in Li-Fraumeni families with wild-type *p53* and associated with a subset of hereditary breast cancer.[21-23] Interestingly, we and others have identified the presence of *CHK2* germ line mutations in MCL patients, suggesting that this gene may also play a role in genetic predisposition to this lymphoid neoplasm.[24,25]

In this report, we describe the first three families of patients with MCL in which a first-degree relative developed a MCL or other lymphoid malignancy. To determine the possible implication of DNA damage response elements in the pathogenesis of this familial aggregation, we analyzed the gene status of ATM, *CHK1*, *CHK2*, and *p53* in these families.

Design and Methods

Case selection

To determine the possible existence of familial lymphoid neoplasms in MCL patients, we searched the clinical records of the 85 MCL patients diagnosed and followed in the Hospital Clinic of Barcelona from 1988 to 2002 and the clinical and pathology databases of lymphoid neoplasms of this institution. We identified two families (2.4%) of MCL patients in which a first-degree relative had developed a lymphoid neoplasm. In addition, a third family from the Massachusetts General Hospital, Boston, MA (USA) was also included in the study. The diagnosis of MCL was established in all cases by characteristic morphology, immunophenotype ($CD5^+$, cyclin $D1^+$) and/or genetic studies demonstrating the t(11;14) translocation.[1,26]

Molecular analysis

High molecular weight DNA was extracted from frozen tissues using proteinase K/RNase treatment and phenol-chloroform extraction. To determine the VH gene family used by the clonal MCL populations, 200 ng of genomic DNA were amplified by polymerase chain reaction (PCR) using six different consensus primers (VH1, VH2, VH3, VH4, VH5, VH6) derived from the framework region 1 (FR1) as sense primers in conjunction with an antisense consensus JH primer as previously described.[27] PCR products were purified and directly sequenced, in both directions to avoid misreading errors, with the appropriate specific VH primer using the Big Dye Terminator Cycle Sequencing 1.1 and 3.1 (Applied Biosystems) in an automated DNA sequencer (ABI PRISM 3100, Applied Biosystems). The sequences obtained were aligned with the published germ line VH, D, and JH genes segments using DNAPLOT or VBASE (*www.mrc-cpe.cam.ac.uk/imt-doc/ or www.ncbi.nlm. nih.gov/igblast*). JH elements and individual DH segments were identified by comparison with published germline sequences. VH sequences showing a mismatch of more than 2% from the corresponding germline gene were defined as mutated.

Total RNA was isolated from frozen samples using the Ultraspec RNA extraction kit (Biotecx, Houston, TX, USA) following the manufacturer's recommendations. The reverse transcription was performed using the Taqman reverse transcription kit (Applied Biosystems, Branchburg, New Jersey, USA) with random hexamer priming and 2.5 μg of the total RNA. The complete coding regions of *ATM*, *CHK1*, *CHK2*, and the p53 exons from 4 to 8 were screened for the presence of gene mutations. *ATM* and *CHK2* genes were amplified by PCR from cDNA in partly overlapping fragments using the primers and conditions previously described.[17,28] The reaction products were directly sequenced using BigDye terminator chemistry on a Perkin-Elmer ABI-377 automated sequencer. The changes were confirmed by sequencing both strands. To examine the prevalence of the *ATM* (D1853N) polymorphic variant in normal Spanish population, a PCR-single-stranded conformational polymorphism (SSCP) analysis was performed. DNA obtained from 50 healthy blood donors was subjected to PCR reactions flanking the genomic region in which the nucleotide substitution is located. The *ATM* gene variant was amplified using the *ATM* forward (5'-TGACTTTTGTCAGACTGTACTTCCA- 3') and reverse (5'-CGTTTGCGAGAAGTGTCG- 3') primers and the following thermocycling conditions: 35 cycles at 94°C for 45 s, 58°C for 45 s, and 72°C for 1 min 30 s. The PCR products were diluted in formamide-dye loading buffer and electrophoresed on a 15% non-denaturing polyacrylamide gel in both the presence and absence of 5% glycerol at room temperature or at 4°C. The gels were developed using a silver staining procedure as previously described.[29]

The *CHK1* gene was examined using a reverse transcription (RT)-PCR-SSCP strategy. PCR reactions of *CHK1* gene were performed in 9 overlapping segments by RT-PCR as described elsewhere.[28] These PCR amplifications were analyzed using a SSCP strategy as described above. To determine the mutational status of p53, the individual exons 4 to 8 were amplified from genomic DNA and screened for mutations using the SSCP strategy previously described.[30,31] PCR products of cases showing altered mobility were directly sequenced using BigDye terminator chemistry (Applied Biosystems).

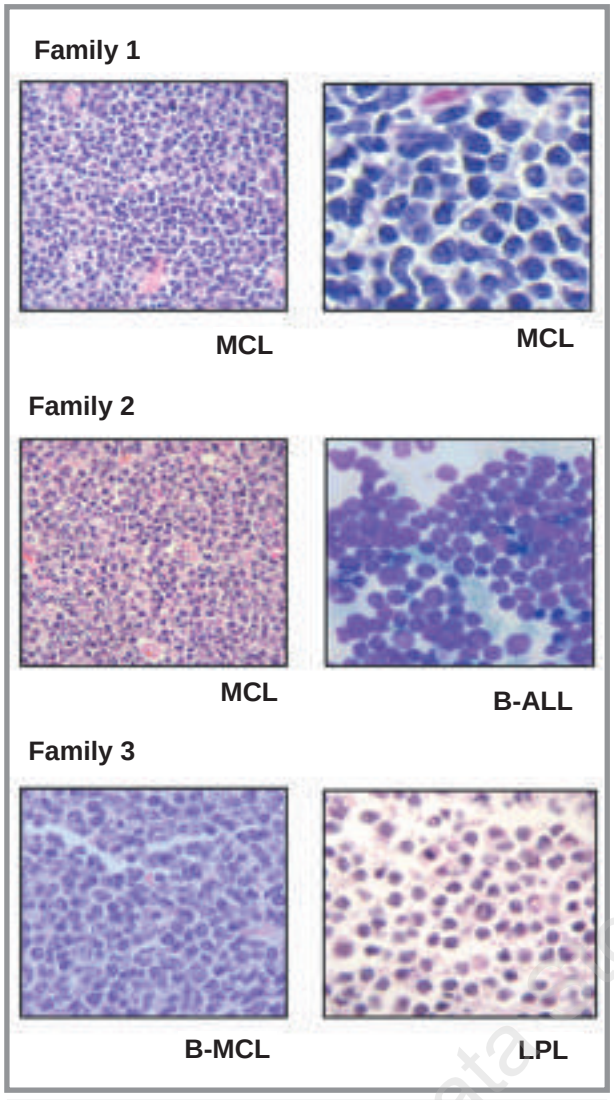

Figure 1. Hematoxylin-eosin stained sections of the hematologic tumors analyzed in this study. In each family, the left picture shows the MCL patient initially diagnosed, and the right the lymphoid neoplasm detected in the first degree relative.

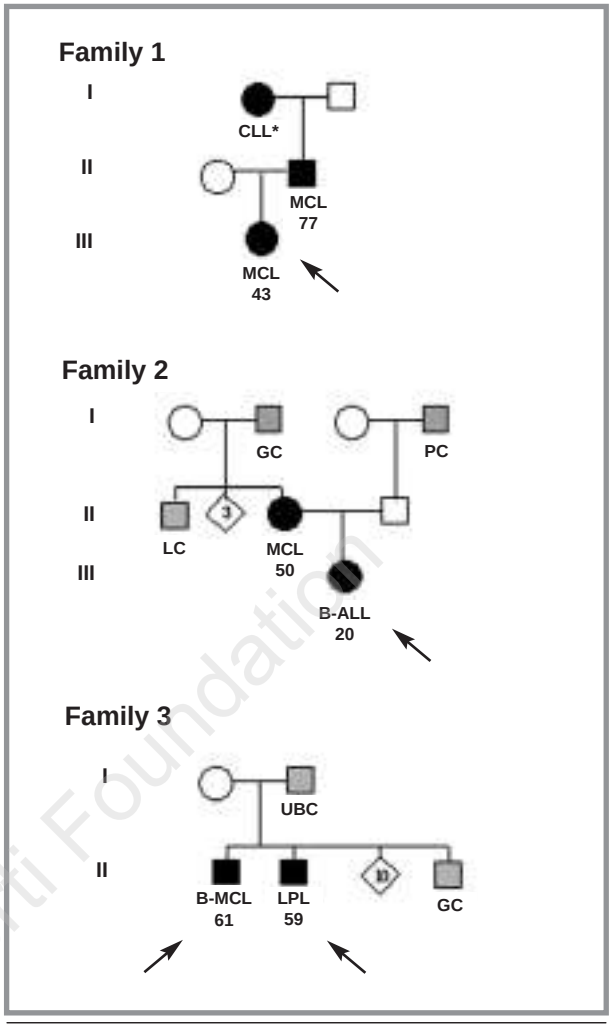

Figure 2. Pedigrees from the families analyzed in this study. Solid circles (females) and squares (males) indicate affected individuals with solid tumors (grey) or lymphoid neoplasms (black). A numbered rhombus is used to join persons independently of their sex, with the number indicating the individual grouped. Arrows point to the individuals in whom molecular studies were performed.

Results

Description of the families

Family 1. A 43-year old female presented with a clonal CD19/CD5/CD23 positive lymphocytosis initially diagnosed as CLL. One year later the disease progressed to a more advanced stage with poor response to fludarabine and CHOP, and she underwent a non-myeloablative allogeneic stem-cell transplant. Fifteen months later, she developed an enlarged right tonsil, which had morphologic and immunophenotypic features of blastoid MCL (cyclin D1$^+$) (Figure 1). Fluorescent *in situ* hybridization (FISH) analysis of the peripheral blood showed a t(11;14) in B cells. PCR and sequencing analysis of the immunoglobulin heavy chain revealed a clonal rearrangement of the VH1-69 gene with no somatic hypermutations. She was treated with a second allogeneic transplant. A relapse was detected in the small bowel 6 months later, treated with resection, ICE chemotherapy, and donor leukocyte infusion, and one year later there was no evidence of lymphoma.

Her father was initially diagnosed with CLL at the age of 77. These slides were reviewed and showed morphologic features identical to those of the patient's initial bone marrow. Although the paraffin blocks were no longer available for cyclin D1 staining or FISH, the neoplasm was considered to be most probably a MCL (Figure 1). There was also a statement in the clinical record that the paternal grandmother had had CLL but these slides were not available for review (Figure 2).

Family 2. A 50-year old female was diagnosed with a stage IV diffuse typical MCL with lymph node, bone

Table 1. Familial lymphoid neoplasms in relatives of MCL patients.

Family	*Patient*	*Tumor Type*	*Age at diagnosis*	*Mutational Analysis ATM, CHK2, CHK1, p53*
1	Grandmother	CLL	NA	ND
	Father	MCL	77	ND
	Daughter	MCL/B-MCL–	43	WT
2	Mother	MCL	50	ND
	Daughter	B-ALL	20	WT
3	Brother	B-MCL	61	*ATM* D1853N*
	Brother	LPL	69	*ATM* D1853N+

*MCL: mantle cell lymphoma, B-MCL: blastoid MCL, ALL: acute lymphoblastic leukemia, LPL: lymphoplasmacytic lymphoma, ND: not done; NA: not available; WT: wild type. *: heterozygous substitution, +: homozygous substitution; —: started with a lymphocytic variant and went on to a blastoid variant.*

marrow, and breast involvement (Figure 1). This tumor showed a clonal rearrangement of the immunoglobulin heavy chain VH4-39 and no somatic hypermutation of the gene. She received treatment with CHOP, achieving only a partial response. The patient underwent an autologous bone marrow transplantation. Three years after this procedure she presented with a bone marrow relapse and was treated with an allogeneic bone marrow transplantation from an identical HLA sibling. Three years later she is in complete response with no molecular evidence of the disease.

Her 20-year old daughter was diagnosed with an acute lymphoblastic leukemia in stage B-IV of differentiation (Figure 1). She presented with an increased WBC count, enlargement of lymph nodes and spleen, and cutaneous lesions. Blastic cells were TdT^+, $sIgM^+$, $CD10^+$, $CD19^+$, $CD24^+$, whereas CD34 was negative. Cytogenetic analysis showed 49 XX, +X, +8, +20, del(11q13) and der22q, whereas the *BCR-ABL* rearrangement analysis was negative. The patient received induction therapy followed by three intensification treatments. Finally, she received an autologous peripheral stem-cell transplantation and remains in complete remission one year after the diagnosis. Interestingly, a review of the clinical record of this family revealed that other relatives had developed different types of non-hematologic neoplasms (Figure 2).

Family 3. A 61-year old male presented in 1988 with atypical lymphocytosis, anemia and thrombocytopenia. The patient was initially diagnosed as having an acute B-cell lymphoblastic leukemia and was subsequently treated with an intensive regimen containing doxorubicin. Although a complete response was achieved, the patient relapsed six months later with generalized lymphadenopathy. At that time a lymph node biopsy was diagnostic of diffuse blastoid MCL with a BCL-1 rearrangement and cyclin D1 overexpression (Figure 1). The initial diagnostic sample was reviewed and reconsidered to show a leukemic phase of a blastoid MCL. The tumor cells had a blastic morphology with expression of B-cell markers and CD5, but TdT was negative. Salvage therapy with CHOP was given, but the patient had a poor response and died 22 months after the diagnosis due to progression of the disease.

His brother, a 69-year old male, presented with an ulceration of the hard palate. Biopsy of this lesion was diagnostic of lymphoplasmacytic lymphoma (Figure 1). All the staging procedures (CT scan, bone marrow biopsy and aspirate) were normal. Protein serum electrophoresis disclosed a small M spike that was of IgM-kappa subtype. The patient was subsequently treated with intermittent doses of chlorambucil and, one year after the diagnosis, there is no evidence of lymphoma. In addition, as for the other families, a review of the clinical records showed that other relatives had been affected by different types of solid tumors (Figure 2).

Molecular analysis

To determine the potential role of DNA damage response genes in the pathogenesis of this familial aggregation, mutational analysis of the *ATM, CHK1*, *CHK2*, and *p53* genes was performed in the three families. These studies were performed in the MCL and ALL of the second generation of families 1 and 2 and the germ line samples of patient 1 and 2 in family 3. No nucleotide changes in *CHK2*, *CHK1*, and *p53* genes were detected in any of the patients analyzed. The unique *ATM* gene change found was a previously described nucleotide substitution A→G at position 5557 (Asp1853Asn). This variant was observed in the germ line of family 3, in homozygosity in patient 2 and in heterozygosity in patient 1 (Table 1). Previous studies suggested that this ATM variant may confer a modest cancer risk.[32] We had previously found this change in 15% of MCL patients.[17] To elucidate whether this variant could be a genetic factor contributing to MCL, we analyzed 50 Spanish healthy blood donors. The frequency of the variant was 15%, which is similar to that in other healthy populations and in our previous series of patients with MCL.[17,32]

Discussion

Several studies have documented familial aggregation of different types of lymphoid neoplasms including CLL, follicular lymphomas, Hodgkin's lymphoma, and multiple myeloma.[3-10] In this study we describe the first families of MCL patients in which a first-degree relative developed a MCL or other lymphoid neoplasms. The patients in family 1 had been initially diagnosed as having CLL but were reclassified as hav-

ing MCL upon review of the tissue biopsies. Many CLL families were reported before MCL was recognized as a distinct entity and some of these familial studies do not identify the specific subtypes of non-Hodgkin's lymphomas diagnosed in different family members. In addition, many epidemiological studies are only based on the review of the pathology reports without a reassessment of the diagnostic samples. Therefore, it is possible that familial lymphoid neoplasms associated with MCL may be more frequent than could be previously suspected. The lymphoid neoplasms which developed in the relatives of these MCL patients included a blastoid MCL, an acute B-cell lymphoblastic leukemia, and a lymphoplasmacytic lymphoma. This heterogeneity in the lymphoid neoplasms diagnosed in familial clusters has been well recognized in CLL and other hematologic neoplasms, suggesting that the potential genetic event involved in hereditary transmission may have a pleiotropic effect acting during an early phase of hematopoietic development.[3,9,33,34] Interestingly, in the two families with involvement of the second generation, the second generation patients developed a more aggressive tumor and at earlier age than their respective parents (Table 1). In family 1, the father had a typical MCL diagnosed at the age of 77, whereas the daughter was diagnosed with a blastoid MCL when she was 43 years old, an early age for MCL in which the median age at diagnosis is usually from 54 to 68.[1] In family 2, an ALL was diagnosed in the 20 year-old daugther, whereas the MCL in the mother was detected at the age of 50, again a relatively early age for diagnosing MCL. This phenomenon of earlier onset and more severe phenotype in successive generations is known as anticipation and has been described in other familial hematologic neoplasms.[35-38]

Although the mechanism of this phenomenon is not understood, different observations suggest that it may be due to a genetic alteration.[9,38] The observations in our study indicate that anticipation also occurs in familial lymphoid neoplasms in MCL patients. Various studies have attempted to elucidate the genetic and molecular mechanisms underlying the phenomenon of familial aggregation in lymphoid neoplasms, particularly in Hodgkin's lymphoma and CLL families. These studies have examined the potential role of HLA genes, CD79b mutations, pseudo-autosomal regions, and immunoglobulin gene usage without clear evidence of linkage for familial clustering in non-Hodgkin's lymphoid neoplasms.[3] Germ-line inactivation of different genes involved in DNA damage response pathways such as ATM and NBS1 have been associated with the development of malignant lymphomas.[39] Li-Fraumeni patients with constitutional mutations of p53 gene, also develop malignant lymphomas albeit less frequently than other neoplasms.[40] Recent studies have identified alterations of *ATM* and *CHK2* genes in sporadic malignant lymphomas including CLL and MCL.[11,17,24,25,41-44] Interestingly, some of these patients carry germ-line mutations of these genes suggesting a potential susceptibility role in the development of these lymphomas.[11,17,24,25,41]

Based on these observations, we analyzed the potential inactivation of the DNA damage response genes *ATM*, *CHK2*, *CHK1*, and p53 in our three families with MCL. However, no mutations were observed in these genes indicating that their inactivation does not account for familial aggregation with MCL. These results are concordant with recent studies on ATM and p53 in familiar CLL and other hematologic malignancies in which inactivation of these genes did not represent major susceptibility targets for familial aggregation.[7,16,18] In our study, the *ATM* gene mutational analysis revealed the presence of the known polymorphic variant D1853N in one of the MCL families analyzed. This nucleotide substitution was detected in the two individuals of this family, in homozygosity in one case and in heterozygosity in the other (Table 1). A previous study had suggested that this *ATM* genetic variant could be associated with an increased risk of cancer in hereditary non-polyposis colorectal cancer.[32] However, we have now observed that the frequency of this polymorphism in a healthy population is 15%, similar to the frequency detected in our previous series of sporadic cases of MCL.[17] This ATM substitution was also present in a subset of familial CLL, but the change did not segregate with the disease.[18] Taken together, these data indicate that this variant is a common ATM polymorphism not associated with a susceptibility to these tumors. In conclusion, this study shows that familial aggregation of lymphoid neoplasms may occur in MCL patients. As in other familial lymphoid clusters, the tumors may be heterogeneous and are associated with the phemomenon of anticipation. The absence of mutations in *ATM* and other DNA damage response elements indicates that these genes do not represent major susceptibility targets in these families.

FT and EC performed the molecular study of the ATM, CHK2, CHK1 and p53 genes in these cases and drafted the first version of the article. FB and EM review the series of MCL patients of our institution, selected the families, and reviewed all the clinical characteristics of these patients, and drafted the clinical aspects of the manuscript. NLH studied and reviewed the clincial and pathological characteristics of the family from Boston. EC reviewed all the pathology samples of the two families from Barcelona, supervised the molecular study, and wrote the final version of the manuscript. EM and EC designed the whole study. All authors reviewed critically the final version of the manuscript. The authors reported no potential conflicts of interest.

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