SHORT COMMUNICATION

Numerous Ontogenetic Roads to Mantle Cell Lymphoma

Immunogenetic and Immunohistochemical Evidence

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To obtain insight into the ontogeny of mantle cell lymphoma (MCL), we assessed 206 patients from a morphological, immunohistochemical, and immunogenetic perspective. Our series included nodal ($n = 151$), extranodal ($n = 28$), and primary splenic ($n = 27$) MCL cases. Skewing of the immunoglobulin heavy variable (IGHV) gene repertoire was noted, with only four IGHV genes accounting for 46% of cases and approximately 70% of cases (107/154) bearing an imprint of somatic hypermutation (SHM) ranging from minimal to pronounced. Interestingly, a distinctive immunophenotypic and immunogenetic profile was identified for primary splenic MCL, which was enriched for DBA.44-positive cases ($P < 0.001$) and used the IGHV1-8 gene more frequently ($P = 0.02$) compared to nodal or extranodal cases, alluding to distinct immunopathogenetic and antigen selection processes. Expression of CD27 (considered a marker of activated B cells) was generally dissociated from SHM and was more prevalent in cases with no or minimal/borderline SHM. These findings support the idea that antigen drive is relevant for most MCL cases, although the specific antigens and the precise location of affinity maturation remain to be elucidated. Moreover, they raise the intriguing hypothesis of multiple cellular origins for MCL. (*Am J Pathol* 2017, 187: 1454–1458; <http://dx.doi.org/10.1016/j.ajpath.2017.02.017>)

Recent molecular and functional evidence supports antigen drive in the pathogenesis of mantle cell lymphoma (MCL).¹ Indeed, MCL is characterized by pronounced immunoglobulin (IG) gene repertoire restriction, culminating in the existence of quasi-identical (stereotyped) antigen receptors,² almost ubiquitous expression of activation-induced cytidine deaminase,³ and some imprint of somatic hypermutation (SHM) in the clonotypic IG heavy variable (IGHV) genes of most (approximately 70%) cases, indicating antigen

interactions.² Furthermore, both relapsed/refractory and treatment-naïve MCL patients exhibit remarkable responses to B-cell receptor signaling inhibitors, alluding to microenvironment triggering in the natural history of MCL.⁴

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Despite the compelling evidence for an antigen-driven origin for most MCL cases, questions abound, especially in relation to whether distinct ontogenetic pathways may lead to the considerable heterogeneity observed within MCL. Herein, we sought to obtain insights into these issues through an integrated histopathological, immunophenotypic, and immunogenetic analysis of a large series of MCL patients.

Materials and Methods

Patients

Two hundred six patients with MCL, diagnosed according to the 2008 World Health Organization criteria, from institutions in Greece, Italy, Spain, and Sweden, were included in the study. On the basis of the primary site of involvement, cases were assigned into three subgroups: i) nodal: 151 cases presented with nodal disease; ii) extranodal: 28 cases in whom the primary site of involvement was located at anatomical sites other than lymph nodes, spleen, or bone marrow; and iii) splenic: 27 cases with primary splenic MCL. All cases displayed a typical MCL immunophenotype and were positive for cyclin D1 expression; no case expressed CD10. The MCL cases of the present study were not systematically tested for the presence of the *CCND1* translocation; that said, all cases with available fluorescence *in situ* hybridization data were positive for this aberration. The study was conducted in accordance with the Declaration of Helsinki and approved by the local Ethics Committee of each institution.

Tissue Samples, Processing, and Immunohistochemistry

The evaluated samples were obtained from the following tissue locations: i) nodal subgroup: lymph node biopsy specimens ($n = 137$) and bone marrow biopsy specimens ($n = 14$) from patients with nodal MCL; ii) extranodal subgroup: biopsy samples from the involved site from patients ($n = 28$) with extranodal MCL; and iii) splenic subgroup: splenectomy specimens ($n = 17$) and bone marrow biopsy specimens ($n = 10$) from patients with splenic MCL. All specimens were formalin fixed and paraffin embedded.

Tissue samples were stained with hematoxylin and eosin for morphological evaluation. Immunophenotyping of neoplastic cells was performed as described previously (Table 1).^{5,6} Immunostaining for CD27, DBA.44, IRF4/MUM1, and surface IG heavy chain were centralized.

Immunoglobulin Gene Repertoire Analysis

PCR amplification and sequence analysis of IGHV-IGHD-IGHJ rearrangements was performed as described previously.²

Statistical Analysis

Descriptive statistics for discrete parameters included counts and frequency distributions. For quantitative variables, statistical measures included means, medians, SD, and minimum-maximum values. The significance of bivariate relationships was assessed by χ^2 and *t*-tests. For all

Table 1 List of the Antibody Panel Used in the Present Study, the Clone, Dilution, Source, and Autostainer Used

Antibody	Clone	Dilution	Source	Device
CD3	2GV6	Ready to use	Ventana-Roche (Basel, Switzerland)	BenchMark XT
CD5	SP19	Ready to use	Ventana-Roche	BenchMark XT
CD10	56C6	Ready to use	Ventana-Roche	BenchMark XT
CD20	L-26	1:100	Dako (Glostrup, Denmark)	Dako Autostainer Link
CD21	1F8	1:20	Dako	Dako Autostainer Link
CD23	1B12	Ready to use	Ventana-Roche	BenchMark XT
CD27	137B4	1:20	Leica (Nussloch, Germany)	BenchMark XT
CD35	RLB25	1:20	Cell Marque (Rocklin, CA)	Dako Autostainer Link
CD43	MT1	1:20	Cell Marque	Dako Autostainer Link
CD79 α	JCB117	1:10	Dako	Dako Autostainer Link
BclII	124	1:20	Dako	Dako Autostainer Link
BclVI	GI191E/A8	1:50	Cell Marque	Dako Autostainer Link
Cyclin D1	SP4	Ready to use	Cell Marque	BenchMark XT
Hairy cell leukemia	DBA44	1:20	Dako	Dako Autostainer Link
IgA	Polyclonal	1:7500	Dako	BenchMark XT
IgD	Polyclonal	1:250	Dako	BenchMark XT
IgG	Polyclonal	1:7500	Dako	BenchMark XT
IgM	Polyclonal	1:5000	Dako	BenchMark XT
κ	Polyclonal	1:7500	Dako	BenchMark XT
λ	Polyclonal	1:7500	Dako	BenchMark XT
TRAP	9C5	1:20	Cell Marque	Dako Autostainer Link
IRF4/MUM1	Mum1p	1:20	Dako	Dako Autostainer Link

comparisons, a significance level of $P < 0.05$ was set, and all statistical analyses were performed with the statistical package, SPSS version 12.0 (SPSS, Chicago, IL).

Results

Herein, we sought to refine our understanding about the role of antigen selection in MCL ontogeny through a combined morphologic, immunohistochemical, and immunogenetic analysis. The well-recognized cytomorphological heterogeneity of MCL was evidenced using hematoxylin and eosin staining with the common variant observed in 124/185 (67%) cases, the blastoid variant in 48/185 (26%) cases, and the pleomorphic variant in 13/185 (7%) cases. No differences were observed regarding the relative frequency of the cytological variants among nodal, extranodal, or splenic MCL.

In all cases, lymphoma cells were immunoreactive for CD5, CD20, CD79a, CD43, BCL2, and cyclin D1, and were consistently negative for CD23, CD10, CD3, and BCL6. Immunohistochemical analysis was extended to include: i) CD27 and IRF4 (MUM1), markers not normally detected in naïve pregerminal center (pre-GC) B cells of the inner mantle zone^{7,8}; ii) DBA.44, which is normally expressed by inner mantle zone cells and a fraction of monocytoid B cells as well as a small proportion of indolent and aggressive B-cell lymphomas (however, not by MCL)⁹; and iii) surface immunoglobulin heavy chains (SIg). The results are detailed in [Supplemental Table S1](#) and summarized as follows: i) 104/193 (53.9%) cases were CD27⁺; ii) 14/158 (8.8%) cases were DBA.44⁺; iii) 46/83 (55.4%) cases were IRF4⁺; and iv) 73/103 (71%) cases were SIgM⁺SIgD⁺, 24/103 (23%) were SIgM⁺SIgD⁻, and 6 were SIgM⁻SIgD⁺ or IgG⁺ (3% each). Of 102 cases with available data, 47 (46%) exhibited a high Ki-67 index ($\geq 30\%$); as previously reported,¹⁰ blastoid and pleomorphic variants were significantly enriched for cases with Ki-67 $\geq 30\%$ [23/25 (92%); and 10/10 (100%), respectively] in contrast to common variant cases [14/57 (24.5%)] ($P < 0.001$). Overall, these results confirm and significantly extend earlier reports regarding the immunophenotypic heterogeneity of MCL,¹¹ while offering novel information about the expressed IG heavy chain isotype.

In keeping with the literature,² the IGHV gene repertoire of the present cohort was remarkably biased, with IGHV3-21 predominating [21/154 cases with available data (13.6%)], followed by the IGHV4-34 [19/154 (12.3%)], IGHV3-23 [16/154 (10.4%)], and IGHV1-8 [15/154 (9.7%)] genes. For the assessment of SHM, all cases bearing differences from the germline, even a single-nucleotide change, were considered as somatically hypermutated. Our decision to follow this strategy rather than adopt the 2% cutoff for germline identity used for prognostication purposes in chronic lymphocytic leukemia^{12,13} is based on ample evidence from studies on various B-cell clones (normal, autoractive, and malignant) that even minimal changes

introduced by SHM can have an important functional impact and, thus, are biologically relevant.¹⁴ On these grounds, we considered separately 47/154 (30.6%) cases with 100% germline identity (truly unmutated) from cases bearing nucleotide changes [mutated, 107/154 (69.4%)]. The latter exhibited a variable load of SHM ranging from minimal to pronounced. More specifically, following our previous definitions,^{1,2} 87/154 (56.5%) cases carried IGHV genes with 97% to 99.9% germline identity and were assigned to a borderline/minimally mutated subgroup, whereas 20/154 (12.9%) cases carried IGHV genes with $<97\%$ germline identity and were assigned to a highly mutated subgroup.

Combined assessment of morphological, immunohistochemical, and immunogenetic results revealed considerable differences between nodal, extranodal, and splenic MCL, as follows. i) No primary splenic MCL case tested ($n = 6$) displayed high ($\geq 30\%$) Ki-67 proliferation index, which was in contrast to 54.5% (42/77) of nodal and 57.8% (11/19) of extranodal MCL cases ($P = 0.03$). ii) DBA.44, a marker of the normal inner mantle zone cells in the lymph nodes, was not detected in any of the 18 extranodal MCL cases analyzed, was rare in nodal MCL [7/118 (5.9%)], whereas, notably, it was highly expressed among primary splenic MCL [7/22 (31.8%); $P < 0.001$ for both comparisons] ([Figure 1](#)). The latter is noteworthy given that DBA.44 is also expressed in the great majority of primary splenic lymphomas of postulated marginal zone origin, although not by normal splenic marginal zone cells.⁵ iii) CD27 expression was more prevalent among cases with minimal/borderline SHM load [50/83 (60%)] or no SHM [21/43 (48.8%)], whereas it was less frequent among cases with a pronounced SHM load [6/19 (31.6%); $P = 0.02$ when compared to minimal/borderline SHM cases] ([Figure 2](#)). The comparison between cases with no SHM and those with pronounced SHM did not suggest a statistically significant difference ($P = 0.2$); however, the absolute difference in percentages was large (17.2%), leading to the assumption that the absence of significance is mainly because of the small size of the available samples (43 and 19, respectively). iv) IGHV gene usage was unevenly distributed depending on the primary site of involvement, with statistically important differences evidenced for IGHV1-8 (expressed by 27.7% of primary splenic cases versus only 7.6% and 5.2% of nodal and extranodal cases, respectively; $P = 0.02$), alluding to the potential role of distinct microenvironmental influences in the ontogeny of MCL.

Discussion

In the present study, we confirm the existence of distinct phenotypical and molecular profiles in MCL, arguing against a single cell of origin for MCL. Moreover, we document that a sizable fraction of MCL cases bearing minimal or no SHM often express CD27, a marker of activated lymphocytes, whereas, in contrast, a fraction of

Figure 1 Patterns of infiltration and cyclin D1 and DBA.44 expression in spleen (A–C) and bone marrow (D–F) specimens. **A:** Lymphoma infiltration of white pulp with expansion to the red pulp [hematoxylin and eosin (H&E)]. **B** and **C:** Cyclin D1 (**B**) and DBA.44 (**C**) positive lymphoma cells. **D:** Paratrabecular and interstitial pattern of lymphoma infiltration (H&E). **E** and **F:** Cyclin D1 (**E**) and DBA.44 (**F**) positive lymphoma cells. Original magnification: $\times 100$ (A–C); $\times 200$ (D–F).

MCL cases with a pronounced SHM burden were negative for CD27. This novel finding of a dissociation between SHM status and CD27 expression may be considered as evidence for the operation of alternative (CD27-unrelated) modes of activation for at least some MCL progenitors, akin to what has been reported previously for other B-cell malignancies.⁵

We also report, for the first time, that splenic MCL cases are enriched for DBA.44-positive cases and show an IGHV1-8 biased gene usage, thus exhibiting immunogenetic and immunophenotypic characteristics distinct from nodal and extranodal MCL and suggesting particular microenvironmental influences in MCL ontogeny. The clinical implications of these observations remain to be elucidated; however, it is relevant to mention that primary

splenic MCL has been reported to follow a more indolent course compared to nodal MCL.^{15,16}

Taken collectively, our findings raise the following possibilities regarding MCL ontogeny and candidate progenitor cells. i) Naïve, pre-GC cells seem plausible progenitors for a minor fraction of MCL cases with unswitched IGs, no SHM, and negative for CD27 [8/61 (13.1%) of the cases in the present series]. In contrast, ii) bona fide memory B cells¹⁷ may represent the cell of origin for the rare MCL cases that express switched IG receptors [3/103 (2.9%) of the cases in the present series]. iii) Moving to IG borderline/minimally mutated, IgM⁺IgD⁺CD27[−] MCL cases, these could originate from a normal B-cell subpopulation intermediate between naïve and GC cells, with a low impact of SHM, and an IgM⁺IgD⁺CD27[−]CD23[−]CD5⁺CD10[−] phenotype.¹⁸ More complex scenarios could pertain to iv) IG-unmutated or borderline/minimally mutated, IgM⁺IgD⁺CD27⁺ MCL cases, which might be derived from B cells maturing in GC-independent but T-cell-dependent pathways, that have been shown to express CD27 and carry limited SHM within their IG receptor genes¹⁹; or, less plausibly, splenic marginal zone cells that display similar immunophenotypic features.²⁰ Finally, v) IgM⁺IgD⁺ MCL cases with a substantial SHM load might originate from B cells participating in early phases of GC reactions, before class switching.²¹ However, this one-to-one matching of MCL subgroups with distinct profiles to particular normal B-cell subpopulations most probably represents an oversimplification, especially given that the transformation process per se may induce aberrant immunophenotypes.²²

In conclusion, on the evidence presented herein, MCL appears as a remarkably heterogeneous disease where different microenvironments, immune pathways, and

Figure 2 Images from two cases within our cohort exhibiting different CD27 expression. **A:** Case 40 (lymph node—nodal subgroup): Strong and uniform expression of CD27 by lymphoma cells. This case was truly unmutated [germline identity (GI), 100%]. **Inset:** Cyclin D1 expression. **B:** Case 117 (bone marrow—nodal subgroup): CD27-negative lymphoma cells. This case was assigned to the heavily mutated group (GI, 96%). **Inset:** Cyclin D1 expression. Original magnification: $\times 400$ (A and B); $\times 200$ (insets).

antigen selection processes, as well as potentially distinct cellular origins, may underlie the development of cases with unique characteristics.

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Supplemental Data

Supplemental material for this article can be found at <http://dx.doi.org/10.1016/j.ajpath.2017.02.017>.

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