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Mantle cell lymphoma

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In 1982, Weisenburger *et al.* first introduced the concept of mantle-zone lymphoma.¹ According to the terminology used at that time, this was regarded as a variant of intermediate lymphocytic lymphoma that proliferated as wide mantles around non-neoplastic appearing germinal centers (GC). One year later, Swerdlow *et al.* found that the pattern described above was part of the spectrum of the centrocytic lymphoma of the Kiel Classification and might correspond to initial lymph node involvement by the tumor.^{2,3} In 1985, Pileri *et al.* reported on 18 cases of small B-cell lymphomas displaying a mantle-fashion growth around reactive GC, which turned out to be quite heterogeneous on closer examination.⁴ In fact, at disease presentation 13 of the 18 cases displayed cytological and immunological findings consistent with centrocytic lymphoma, while the remaining ones corresponded to neoplasms that nowadays would be diagnosed as marginal zone lymphoma. Interestingly, the centrocytic lymphomas were CD5⁺, FMC7⁺ and CD10⁻ and showed progression to a diffuse growth pattern in follow-up biopsies. Two important conclusions were reached: (i) the mantle-fashion growth was produced by different types of B-cell lymphoma and could not be used as a diagnostic criterion, and (ii) conversely to what is reported in the Kiel Classification,³ centrocytic lymphomas are derived from a normal counterpart other than GC, possibly related to mantle cells. In 1992, the International Lymphoma Study Group (ILSG) made

its first experiment to overcome the discrepancies in terms of lymphoma classification that had hampered communication across the Atlantic for some decades.⁵ In particular, the American and European ILSG members agreed on the existence of a tumor derived from mantle B cells that was consequently termed *mantle-cell lymphoma* (MCL). The criteria for its recognition were drafted and included 2 years later in the Revised European-American Lymphoma Classification that led the way to the latest edition of the World Health Organization (WHO) Classification of Tumours of Haematopoietic and Lymphoid Tissues.^{6,7} The present article will focus on the diagnosis and bio-pathology of MCL in the light of the criteria of the WHO Classification⁷ and recent reports in the literature including those of Quintinilla-Martinez *et al.*, Mozos *et al.* and Dictor *et al.* in this issue of the journal.⁸⁻¹⁰ It will not include the still ongoing debate on the multiple options proposed for the treatment of MCL patients, which often have limited efficacy (comprehensively reviewed by Ghielmini *et al.*).¹¹

Definition

MCL is a distinct entity, representing from 3-10% of non-Hodgkin's lymphomas and more frequently affecting middle-aged to older males (male:female ratio = 2-7:1).^{7,12} It is listed among peripheral B-cell lymphomas, is usually composed of small to medium-sized elements with irregular nuclear contours and *CCDN1* transloca-

tion, and is thought to stem from peripheral B cells of the inner mantle-zone of secondary follicles, mostly of naïve pre-GC type.^{7,12} MCL is generally regarded as an aggressive, incurable disease with the median survival of affected patients being 3-4 years.¹²

Clinical features

MCL more often presents in stage III-IV with lymphadenopathy, hepatosplenomegaly, bone-marrow involvement, and leukemic spread.^{7,12} The latter two findings can be missed by morphological studies alone and are shown by, respectively, immunohistochemistry and FACS analysis in most if not all instances.^{7,12} Waldayer's ring and the gastro-intestinal tract are frequently affected.^{7,12} Most cases of multiple lymphomatous polyposis correspond to MCL.

Morphology

MCL usually consists of small to medium-sized lymphoid elements with irregular nuclear contours, somewhat dispersed chromatin, inconspicuous nucleoli, and scant cytoplasm.^{7,12,13} Within this context, centroblasts, immunoblasts, prolymphocytes and para-immunoblasts are not encountered. This is relevant for the differential diagnosis from follicular lymphoma, lymphoplasmacytic lymphoma and chronic lymphocytic leukemia/small lymphocytic lymphoma, which by definition, contain centroblasts, immunoblasts and prolymphocytes/para-immunoblasts, respectively. Comprised within the neoplastic population, hyaline small vessels and/or epithelioid histiocytes are frequently found. Clusters of plasma cells can be seen: they are usually reactive (polytypic at immunohistochemistry), only exceptionally representing a feature of tumor differentiation with obvious monoclonality and tendency to accumulate in the center of lymphomatous nodules.¹⁴ The number of mitotic figures varies, although it is usually low to moderate (see below).

In the lymph node, spleen and Waldayer's ring, neoplastic cells give rise to a mantle-fashion, nodular or – more frequently – diffuse growth pattern.^{7,12,13} Notably, repeated biopsies demonstrate that such patterns correspond to disease progression. In fact, in the early phases the tumor substitutes the mantle-zone; then, it invades reactive GC producing a nodular pattern; finally, the nodules merge together causing diffuse effacement of the organ's structure. The bone marrow can be variably involved: paratrabecular infiltrates are the commonest finding.

Besides the classical type described above, there are some cytological and/or morphological variants of MCL that can cause diagnostic problems. These are termed blastoid, pleomorphic, small cell, and marginal zone-like.^{7,12,13} The first consists of slightly larger cells resembling lymphoblasts with dispersed chromatin and a high mitotic rate. Blastoid MCL is clinically aggressive, as is the pleomorphic form, which is characterized by a cell population that is highly variable in size and shape, with frequent mitotic figures and a proportion of rather large elements showing oval to irregular nuclear contours, pale cytoplasm and at times prominent nucleoli. Both the blastoid and pleomorphic forms occur rarely

representing morphological progression of the disease. The small cell variant is composed of small, round lymphocytes with more clumped chromatin, mimicking chronic lymphocytic leukemia/small lymphocytic lymphoma. Occasionally, the small lymphomatous elements can be almost exclusively restricted to the inner mantle zones or to narrow mantles, a pattern termed *in situ* MCL and thought to have a more indolent behavior.¹⁵ Finally, the marginal zone-like subtype displays prominent foci of cells with abundant pale cytoplasm resembling marginal zone or monocytoid B-elements.^{7,12} Notably, these cases are at times characterized by splenomegaly, intrasinusoidal bone-marrow infiltration and a leukemic picture in the absence of lymph node involvement. They can be easily confused with splenic marginal zone lymphoma and seem to have a very indolent course. As for *in situ* MCL, the diagnosis of this rare form of the tumor is feasible only upon immunohistochemical detection of cyclin D1 (see below).

Immunophenotype

MCL is characterized by expression of the B-cell markers CD19, CD20, CD22, CD79a and BSAP/PAX5.^{7,12,13} Notably, CD20 is strongly expressed on the surface of neoplastic cells, a feature that can be useful for the differential diagnosis from chronic lymphocytic leukemia/small lymphocytic lymphoma, which shows weak CD20 positivity in the small cell component.¹⁵ The search for immunoglobulin (Ig) heavy and light chains usually reveals IgM/D positivity with more frequent lambda restriction.^{7,12} Neoplastic cells are usually CD5⁺, FMC-7⁺, BCL-2⁺, CD10⁺, BCL-6⁺, and IFR4⁺, with occasional weak expression of CD23.^{7,12,13} In the cases with nodular growth, residual GC cells (CD10⁺, BCL-6⁺) can be detected admixed with the neoplastic population. Furthermore, aberrant phenotypes have been reported in MCL (such as negativity for CD5 and positivity for CD10 and/or BCL-6), sometimes associated with the blastoid/pleomorphic variants or occurring in conjunction with *BCL6/3q27* translocations.⁷ Stains for CD21 and CD35 usually show loose follicular dendritic cell meshworks. In the light of this, although the phenotypic profile of MCL is distinctive, it is not entirely pathognomonic and as such cannot always assist in the differentiation of MCL from follicular lymphoma, lymphoplasmacytic lymphoma, marginal zone lymphoma and chronic lymphocytic leukemia/small lymphocytic lymphoma. For this purpose, the most useful examination is the strong expression of cyclin D1, which is never found in the above mentioned categories of B-type non-Hodgkin's lymphomas.^{7,12,13} This attribute is sustained by the t(11;14)(q13;q32) translocation (see below).^{7,12,13} Notably, cyclin D1 expression is lacking in a small percentage of cases of MCL: because of practical and conceptual implications, these cases will be treated separately (see below). Last but not least, cyclin D1 expression is found in hairy cell leukemia (although weak) and in about 16% of plasma cell myelomas, also carrying t(11;14)(q13;q32).¹⁵ When commercially available, the antibody produced by one of the authors (Eclini)¹⁶ and raised against the IP1A-1

receptor physiologically expressed by marginal zone B-cells, could represent a further tool to aid the differential diagnosis between MCL (IRTA-1⁻) and nodal marginal zone lymphoma (IRTA-1⁺ in about 80% of cases).¹⁷

The t(11;14)(q13;q32) translocation

The t(11;14)(q13;q32) translocation is regarded as the primary genetic event in MCL.^{7,12} It can easily be demonstrated by fluorescent *in situ* hybridization (FISH) and involves the Ig heavy chain gene (*IGH@*) at the 14q32 locus and a region at 11q13 designated *BCL1*.¹² The expression of *CCND1*, located in the latter and encoding for cyclin D1, is deregulated by the translocation.^{7,12} This causes over-expression of cyclin D1 both at the mRNA and protein levels in MCL. Cyclin D1 plays an important role in the cell cycle regulation of G₁-S transition following mitotic growth factor signaling.⁷ Unlike in MCL, in normal cells cyclin D1 is transiently expressed and binds to CDK4 and CDK6 to form a CDK/cyclin complex able to phosphorylate the tumor suppressor gene retinoblastoma (*RB1*) facilitating cell cycle progression.¹² Deregulated expression of cyclin D1 is thought to overcome the effect of *RB1* and *p27/kip*, leading to the development of MCL.^{7,12} Some tumors over-express shorter cyclin D1 transcripts, usually generated by secondary 3'

rearrangements in the *CCD1* locus.^{7,12} These truncated transcripts cause very strong protein expression, high proliferative activity and a more aggressive clinical course.^{7,12}

Notably, it has been reported that inactivating mutations of the *ATM* and/or *CHK2* genes (recorded in 40-75% of MCL) are at times found in the germline of some patients.^{7,12} This might be relevant to the development of the tumor: in fact, such mutations cause deregulation of the DNA damage response pathway and increased genomic instability.^{7,12} In particular, t(11;14) – which should affect immature/naïve B cells as suggested by its detection in the peripheral blood of 1-2% of healthy individuals – would occur in the setting of a population carrying these mutations and lead to constitutive deregulation of cyclin D1 and early expansions of tumor B cells in the mantle zone of lymphoid follicles. This might also explain why MCL is one of the malignant neoplasms with the highest level of genomic instability, which might cause additional oncogenic events needed for the expansion of MCL cells with classical morphology, as well as alterations of genes involved in cell cycle regulation and senescence regulatory pathways that would lead to more aggressive variants of MCL.^{7,12,18} In particular, there is a high number of non-

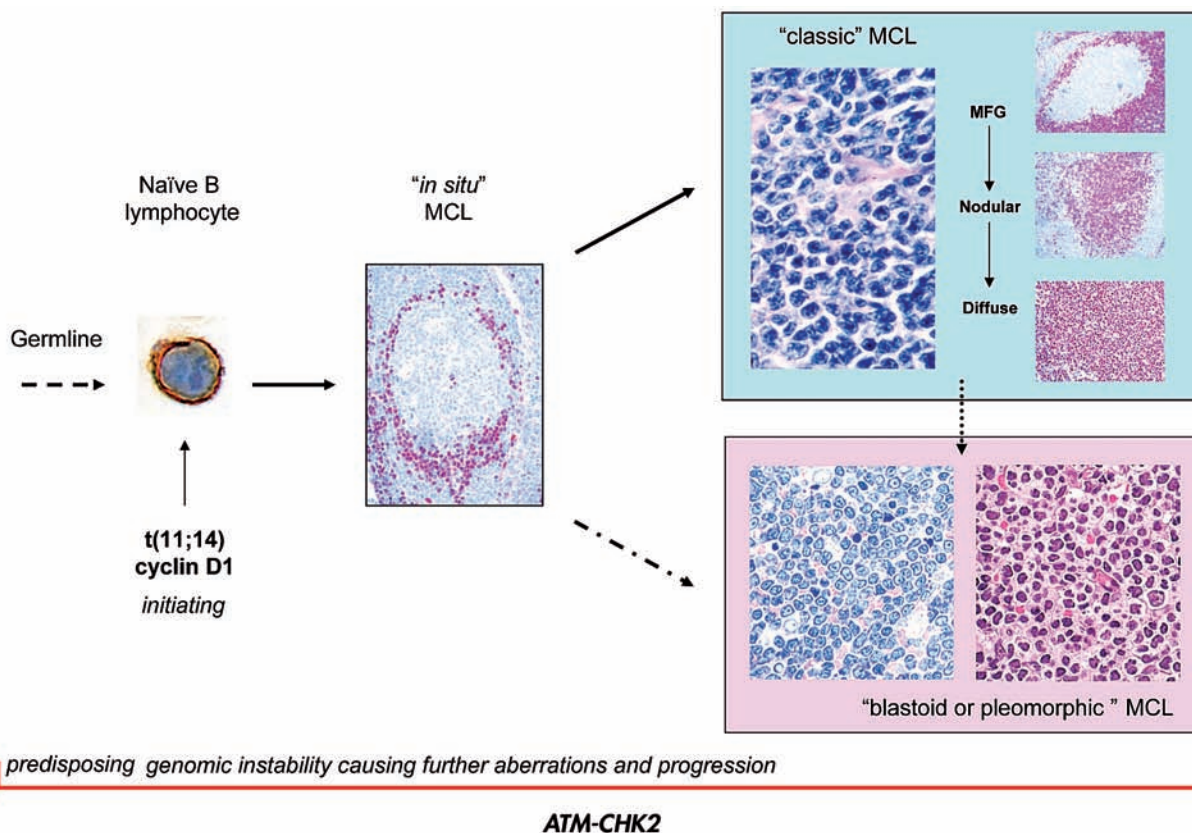


Figure 1. Schematic representation of the postulated steps of the pathogenesis of MCL, shown in conjunction with the main immunomorphological findings. The red immunostain, corresponds to cyclin D1 determined by the alkaline phosphatase anti-alkaline phosphatase complexes technique. The naïve B-lymphocyte is stained for CD20 by immunoperoxidase. The examples of “classic” MCL and “blastoid” MCL are stained with Giemsa, while the “pleomorphic” one is stained with hematoxylin and eosin.

random secondary chromosomal aberrations in MCL, including gains of 3q26, 7p21 and 8p24 (*MYC*), and losses of 1p13-p31, 6q23-q27, 9p21, 11q22-q23, 13q11-q13, 13q14-q34, and 17p13-ter.^{7,18} Trisomy 12 is detected in about 25% of cases. Tetraploid clones are more common in the pleomorphic and blastoid variants than in the classical type (80%, 36% and 8%, respectively).^{7,12} t(8;14)(q24;q32) involving *MYC* is rare, but associated with a more aggressive clinical course. Finally, MCL carries frequent mutations of *TP53*, homozygous deletions of the *INK4a/ARF*, amplifications of the *BMI1* polycomb and *CDK4* genes, and occasional micro-deletions of the *RB1* gene, all producing high proliferative activity.^{7,12}

The possible steps of the molecular pathogenesis of MCL are outlined in Figure 1 in relation to immunomorphological findings.

Antigen receptor genes

Ig genes are rearranged. *IGH@* genes are unmutated in most cases, although mutations are found in a minority of MCL.^{7,12} The load of the latter is lower than in mutated chronic lymphocytic leukemia.^{7,12} In addition, in MCL *IGH@* somatic mutations do not correlate with *ZAP70* expression and survival.^{7,12} A biased usage of *IGH@* genes has been reported in some cases, suggesting that MCL may originate from specific B-cell subsets. Unlike in chronic lymphocytic leukemia, in MCL *VH3-21* usage occurs in unmutated cases and bears a lower amount of genomic imbalances and a better prognosis.⁷

Gene expression profile

In 2003, the Lymphoma/Leukemia Molecular Profiling Project group showed that MCL has a specific gene signature that differs from the signatures of small lymphocytic lymphoma and diffuse large B-cell lymphoma of both the GC B cell-like and activated B cell-like types.¹⁹ Interestingly, this signature encompassed the usual cyclin D1-positive cases and a small subgroup of cyclin D1-negative MCL. Besides elucidating the pathogenesis of the tumor, the gene expression profile (GEP) revealed 20 proliferation-associated genes whose expression measurement identified subsets of patients whose median survival differed by more than 5 years. Differences in cyclin D1 mRNA abundance synergized with *INK4a/ARF* locus deletions to dictate tumor proliferation rate and survival. Two years later, the same group reported on six cases of MCL lacking cyclin D1 that exhibited the same clinical, morphological and GEP features as classical MCL but did not carry the t(11;18)(q12;q32), as determined by FISH.²⁰ These cases did, however, express either cyclin D2 or cyclin D3 at both the mRNA and protein levels, suggesting that up-regulation of these cyclins may substitute for cyclin D1 in the pathogenesis of MCL.

Cyclin D1-negative mantle cell lymphoma

Since cyclins D2 and D3 are also expressed by normal B cells and most, if not all, B-cell non-Hodgkin's lymphoma,⁸ although at lower levels,¹² these markers cannot be confidently used for differentiating cyclin D1-negative MCL from other small B-cell tumors.^{8,12} In

2008, this led Campo *et al.* to conclude that "the only reliable criteria to establish the diagnosis of cyclin D1-negative MCL seemed to be the microarray profile that is limited to research environments".¹² In this issue of the journal, three reports focus on tools that can allow the easy identification of such cases and can be applied in most histopathology laboratories.⁸⁻¹⁰ First of all, Quintinilla-Martinez *et al.* propose FISH analysis and/or quantitative reverse transcriptase polymerase chain reaction as a means for making the differential diagnosis of cyclin D1-negative MCL.⁸ This approach is based on the one hand on previous observations of *bone fide* cyclins D1⁻/D2⁺ MCL carrying translocations involving the *CCND2* locus with either the *IGK@* [t(2;12)(p12;p13)] or *IGH@* locus [t(12;14)(p13;q32)], not recorded in either chronic lymphocytic leukemia or CD5⁺ mantle zone lymphoma, and, on the other hand, on the at least 10-times higher mRNA levels of cyclin D2 in D1⁻/D2⁺ MCL in comparison with normal lymphoid tissue, follicular lymphoma, mantle zone lymphoma and chronic lymphoma and chronic lymphocytic leukemia.⁸ Mozos *et al.* candidate the expression of the neural transcription factor *SOX11* as a powerful biomarker for the identification of cyclin D1-negative MCL.⁹ In fact, GEP showed significantly higher expression of the *SOX11* gene in classical MCL than in Burkitt's lymphoma, diffuse large B-cell lymphoma, primary mediastinal B-cell lymphoma and follicular lymphoma.⁹ However, one third of cases of Burkitt's lymphoma revealed *SOX11* mRNA levels similar to those in MCL, thus indicating that *SOX11* over-expression is not restricted to MCL.⁹ These findings were corroborated by immunohistochemical studies that showed nuclear *SOX11*-positivity in most, if not all, MCL tested, including 12 cyclin D1-negative cases.⁹ Interestingly, 25% of Burkitt's lymphomas, all examples of B- and T-lymphoblastic leukemia/lymphoma, one classical Hodgkin's lymphoma and 2/3 T-prolymphocytic leukemias also turned out to be positive.⁹ Equivalent results were reported by Dictor *et al.*, who immunostained 172 specimens for the *SOX11* N and C termini.¹⁰ Their findings indicate that *SOX11* can represent a useful tool for the differentiation of MCL from other small B-cell lymphomas in general but is certainly of pivotal importance for identifying the cyclin D1-negative cases. Of course, it should be integrated in a panel of markers in order to avoid any confusion between a potential cyclin D1-negative blastoid MCL and lymphoblastic leukemia/lymphoma, which may be confused morphologically but are easily differentiated by the global phenotypic profile.

Prognostic factors

Apart from the rare forms with an indolent behavior reported above, MCL has a particularly poor outcome.^{7,12} Several attempts have been made to subdivide patients into different risk groups. In particular, the European MCL Network has shown that the number of mitotic figures and Ki-67 marking can allow the identification of three subgroups with different proliferation rates (mitotic indices: <25, 25-49, and >50/mm² and Ki-67 indices: <10%, 10-40%, and >40%, respectively) signif

icantly different outcomes.²¹ Such differences are conserved in advanced-stage MCL patients treated with anti-CD20 immuno-chemotherapy.²² Interestingly, these findings are in keeping with the above reported GEP data¹⁹ and point to the prognostic value of proliferation in MCL. Additional bio-pathological adverse prognosticators – which may be independent of proliferative activity – have been reported, such as blastoid/pleomorphic morphology, trisomy 12, karyotype complexity, *TP53* mutation/over-expression/loss, gains of chromosome 3q, deletions of 9p, and a series of clinical parameters including overt peripheral blood involvement.^{7,12} Recently, a clinical MCL index (MIPI), based on age, ECOG, performance status, lactate dehydrogenase values and leukocyte count, and a five-gene model (*RAN*, *MYC*, *TNFRSF10B*, *POLE2*, and *SLC29A2*) applicable to both frozen and routine samples and based on quantitative reverse transcriptase polymerase chain reaction analysis, have been proposed as further prognostic indicators.^{23,24}

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