Mantle Cell Lymphoma

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Introduction

Mantle Cell Lymphoma (MCL) is a mature B-cell neoplasia that has been well characterized in the last years. The recognition of the t(11;14)(q13; q32) and cyclin D1 overexpression as the genetic and molecular hallmarks of the tumor have been key elements to identify the broad spectrum of clinical, pathological and biological manifestations of the disease (Jares et al 2012). The term mantle cell lymphoma reflects the idea that the normal cell counterpart of this tumor is a lymphocyte whose physiological microenvironment is the mantle zone of the secondary lymphoid follicle. This view is supported by the tendency of the tumor cells to grow and expand this area and to express a phenotype also found in a subset of mantle cells. MCL is considered clinically one of the most aggressive lymphomas with short responses to current therapies, frequent relapses and a relatively short median survival. This behavior has lead to recommend intense therapeutic regimens and explore new strategies with more recent developed drugs targeting specific pathogenetic mechanisms. In spite of the well characterization of MCL, recent molecular studies and clinical observations are opening new perspectives on the ontogeny and pathogenesis of this lymphoma that challenge some of our previous ideas about the disease (Jares et al 2012).

Pathological and molecular characteristics

MCL may grow in three architectural patterns: mantle zone, nodular, or diffuse. The classical cytology is characterized by a monotonous expansion of small to medium-sized lymphoid cells with irregular nuclei. Some cases may show a predominance of small lymphocytes with rounded nuclei (small cell variant) that may be difficult to distinguish from chronic lymphocytic leukemia/small lymphocytic lymphoma (CLL/SLL). Blastoid and pleomorphic cytological variants, resembling lymphoblasts or irregular large cells, respectively, have been associated with more aggressive clinical behavior. All these morphological variants should be considered as ends of a spectrum and some tumors may show overlapping cytological features. Particularly, some cases may show transitional areas between classical and pleomorphic variants with cells that may be difficult to define whether they are classical or pleomorphic. In occasional cases areas of classical and pleomorphic morphology may be identified in different parts of the same lymph node. Blastoid and pleomorphic variants have a higher proliferative activity than classical or small cell variants although some tumors with a classical morphology may show a relatively high mitotic index similar to the blastoid variants.

The usual phenotype of these tumors corresponds to a mature B-cell coexpressing CD5 and CD43. Germinal centers markers such as CD10 and BCL6 are usually negative. The cells tend to express lambda light chain more frequently than kappa. The meshwork of follicular dendritic cells is abundant and disorganized. Some tumors may show aberrant phenotypes lacking CD5 or expressing CD10 or BCL6. The immunohistochemical detection of cyclin D1 is the diagnostic hallmark of this tumor.
Mantle cell lymphoma is genetically characterized by the t(11;14) translocation that deregulates cyclin D1. The role of cyclin D1 in promoting MCL lymphomagenesis may be initially related to its function in the cell cycle regulation by binding to CDK4/6 and phosphorylation of the retinoblastoma protein (RB1) that releases the transcription factor E2F triggering entry into the S phase of the cell cycle. However, several observations suggest that cyclin D1 deregulation is not sufficient for cell transformation nor does it explain the aggressive behavior of MCL. Secondary chromosome alterations targeting genes involved in molecular pathways like cell cycle control, DNA damage response and cell survival pathways are frequently found in aggressive MCL. The INK4a/CDK4/RB1 and ARF/MDM2/TP53 cell cycle pathways are very frequently targeted by secondary genetic alterations in MCL. The CDKN2A locus (9p21), which encodes for both the CDK inhibitor INK4a and the positive p53 regulator ARF, is frequently deleted in MCL. TP53 and RB1 are also frequently inactivated by point mutations and gene deletions. In addition, gene amplification deregulate additional genes including CDK4, polycomb ring finger gene BMI1, and MDM2. Accordingly, the proliferation gene expression signature is the best predictor of patient survival, underscoring the importance of cell cycle deregulation in dictating the behavior of MCL (Jares et al 2012).

The high number of chromosome aberrations observed in MCL is consistent with the frequent deregulation of the DNA damage response in this lymphoma. The ataxia-telangiectasia mutated gene (ATM), located at 11q22-23, is frequently deleted and mutated in MCL cases with increased genomic instability. Recent studies have also shown that genes involved in cell survival are targets of recurrent genetic alterations in MCL. Amplifications and overexpression of antiapoptotic genes such as BCL2 (18q21) and homozygous deletions of proapoptotic genes such as BCL2L11 (2q13) have been described in primary tumors (Jares et al 2012). A recent study has found NOTCH1 mutations in 12% of MCL associated with poor survival. These mutations occur in the PEST domain and generate a truncated more stable and transcriptionally active protein. Inhibition of this pathway reduced proliferation and induced apoptosis of MCL cells.

Cyclin D1-negative Mantle cell lymphoma

Given the relevance of the t(11;14) translocation and cyclin D1 deregulation in MCL, it was very puzzling for pathologists to recognize some lymphomas with the morphological and phenotypic features of MCL that were negative for cyclin D1 expression and they also lacked the t(11;14) translocation. These tumors have a similar gene expression profile and share the same type of secondary chromosomal alterations, supporting the idea that they corresponded to the same molecular disease (Fu et al Blood 2005). However, the lack of a reliable biomarker to identify this variant of MCL had hampered its characterization. SOX11, a neuronal transcription factor, has been identified as a relatively specific marker of MCL since it is highly expressed in virtually all these tumors whereas it is negative in normal lymphocytes at any stage of differentiation and other mature lymphoid neoplasms with the exception of a subgroup of Brukitt lymphoma and lymphoblastic lymphomas (Ek et al Blood 2008; Diktor et al Haematologica 2009; Mozos et al Haematologica 2009). Interestingly, SOX11 is expressed in cyclin D1 negative MCL (Mozos et al Haematologica 2009). The use of this marker has allowed the recognition of an increased number of cases and a better characterization of their pathological, genetic and clinical features (Salaverria et al Blood 2012). SOX11 expression has identified some cyclin D1 negative MCL with a typical mantle zone growth pattern and also blastoid variants emphasizing its relationship with conventional cyclin D1 positive tumors (Salaverria et al 2012; Zeng W et al 2012). Interestingly, 55% of the cyclin D1 negative tumors carry CCND2
rearrangements, in particular with the light chain genes more than IGH but CCND3 translocations have not been found. CCND2 mRNA levels were high in cases carrying the translocation but not in cases negative for the translocation. Cyclin D1 negative MCL had a global genomic profile and high complexity similar to cyclin D1 positive tumors and they also presented clinically with generalized lymphadenopathy, advanced stage, frequent extranodal involvement and had a poor outcome. Similar to conventional cyclin D1 positive MCL, 17p deletions and high Ki67 index conferred a significant worse prognosis. All these findings indicate that cyclin D1-negative tumors are clinically and biologically similar to conventional MCL. Although the translocation of CCND2 may be an oncogenic substitute for CCND1, the absence of these translocations in 45% of the cases leaves open the question of the initial oncogenic event in these tumors. The high expression of SOX11 in all these tumors suggests that, in addition to its value as a diagnostic biomarker, it may be an important factor in the pathogenesis of MCL.

Cell(s ?) of origin and Ontogeny

Recent studies have also challenged the classical idea of MCL as derived from naïve B-cells based on IgM/IgD and CD5 expression by the tumor cells, their topographic distribution in the mantle zones, and early descriptions of the predominant use of unmutated IGHV. More recently, comprehensive analysis of BCR diversity in MCL has shifted this view to a more complex ontogenetic model in which antigen selection plays an important role in pathogenesis, at least for a subset of tumors (Hadzidimitriou, A et al 2011). Recent studies have shown that 15-40% of MCL carry IGHV hypermutations with a strong bias in the IGHV gene repertoire. As it is the case for chronic lymphocytic leukemia (CLL), stereotyped heavy complementarity-determining region 3 (VH CDR3) sequences have been recognized in 10% of MCL. Although the stereotyped subsets are clearly distinct from those described in CLL, their existence suggests a strong role of antigen-driven selection in the clonogenic expansion of MCL tumor cells. These findings open a complex scenario with more than one possible cell subtype dominating in different subtypes of MCL. In the absence of IGHV mutations, MCL may still derive from naïve B cells, but cases with stereotyped BCR were likely antigen selected. Further, MCL carrying a high mutational load may originate from cells strongly influenced by the germinal center microenvironment. Finally, the progenitor cells of cases with low number of somatic mutations may derive from cells of the marginal zone, intermediate cells between naïve and germinal center cells already expressing AID or transitional B cells resembling murine B-1 B cells.

The clinical and biological impact of the IGHV mutational load in MCL has been controversial, probably due to the relative low representation of cases with IGHV hypermutations in most of these studies that have hampered their proper evaluation. MCL with different IGHV mutational status differ in the VH usage and other clinical and pathological characteristics (Navarro et al 2012). MCL with high number of mutations tend to be more frequently CD5 and SOX11 negative, have small cell morphology and non-nodal leukemic presentation, and they also seem to have a better outcome, suggesting that they may correspond to a clinical and biological subtype of the disease.

Initial steps and progression in MCL development

Cells carrying the t(11;14) translocation have been detected at very low levels in the peripheral blood of a number of healthy individuals (8%). These clones can persist for long periods, but their potential to evolve into an overt lymphoma is not clear. Their high frequency in healthy individuals and low prevalence of MCL suggests
that most clones bearing only the t(11;14) translocation will never transform into a malignant tumor. An intriguing recent observation has reported the simultaneous development of MCL with the same clonal origin in a recipient and donor 12 years after an allogenic bone marrow transplant underscoring the long latency required by initial clones to develop an overt lymphoma (Reviewed in Jares et al 2012).

The presence of cells overexpressing cyclin D1 and carrying the t(11;14) translocation have been occasionally found in the mantle zones of otherwise reactive lymphoid tissues in healthy individuals but its prevalence must be very low since a systematic analysis of cyclin D1 in reactive lymph nodes of more than 200 patients did not find any of these lesions (Adam et al 2012, Carvajal-Cuenca et al 2012). Although they were named initially in situ MCL, their malignant potential seems very limited. In a recent study, only 1 out of 12 of these lesions developed an overt MCL 4 years after its detection (Carvajal-Cuenca et al 2012). To avoid overtreatment, the term “in situ MCL-like B-cells” instead of “in situ MCL” has been proposed. Retrospective analysis of reactive lymphoid tissues in MCL patients had identified in situ lesions in most of the patients with an interval between these samples between 2 and 15 years, suggesting that all MCLs proceeded through a stage of in situ lesions. Some in situ lesions express SOX11 whereas others are negative, suggesting that the in situ lesion stage may be a common step in both SOX11-negative and positive subtypes of MCL (Carvajal-Cuenca et al 2012).

**Indolent MCL**

Most patients with MCL present with generalized lymphadenopathy, disseminate disease and follow an aggressive clinical evolution. Some observations indicate, however, that some patients may have a more indolent clinical course (Martin et al 2009). The recognition of these patients is important because they may benefit of a more conservative management for some time without apparently harming their global outcome. Studies of prognostic factors in MCL have indicated that tumors with very low proliferation fraction, limited-stage, or a mantle zone pattern may have a significant better prognosis with longer survival than the global series of patients. These cases may have a conventional phenotype CCND1-positive, SOX11-positive (Jares et al 2012).

In addition to these parameters, clinical observations have recognized a subgroup of MCL patients with an indolent behavior that presented with a non-nodal disease, splenomegaly, and a leukemic phase (Orchard J et al 1999). The gene expression profile of these cases is molecularly more similar to conventional MCL than to any other type of leukemic lymphoid neoplasia. However, they have also a differential expression of a signature of genes that included among others the lack or low levels of SOX11 (Fernandez V et al 2010; Ondrejka SL 2011). Other biological differences were the predominance of highly mutated IGHV and very simple karyotypes in the indolent tumors. In apparent conflicting observations, some studies have found a poor outcome in patients with SOX11-negative MCL (Nygren et al 2012). However, these cases frequently have TP53 alterations including, deletions, mutations or high level of protein expression suggesting that they may correspond to a progressed phase of the indolent tumors similar to the progression or transformation associated with p53 inactivation in other small B-cell lymphomas (Nygren et al 2012, Royo et al 2012). These findings suggest that MCL with a predominant non-nodal and leukemic disease, frequently associated with splenomegaly, and low/negative expression of a particularly signature of genes including SOX11 may correspond to a different molecular subtype of MCL. These tumors may have a long indolent phase and eventually some of them may
progress to a more aggressive tumor associated with the acquisition of additional oncogenic events, such as p53 inactivation (Royo et al 2012, Navarro et al 2012).

**SOX11, an oncogenic driver in MCL**

The constant expression of SOX11 in most MCL, including cases negative for CCND1 or CCND2 translocations, and its virtually absence in the subtype of tumors with a very indolent behavior suggest that SOX11 may contribute to the pathogenesis of this lymphoma and its aggressive clinical behavior. This idea has been recently supported by an experimental MCL-xenotransplant mouse model in which silencing SOX11 in MCL cell lines resulted in a marked and significant reduction in the tumor growth (Vegliante MC et al Blood 2013). A genome wide analysis of the transcriptional program regulated by SOX11 in MCL cell lines has shown that this gene blocks the terminal differentiation of mature B-cell by sustaining the expression of PAX5 and regulates gene programs of cell cycle modulation, apoptosis and stem cell development. This effect of SOX11 may explain the marked cytologic monomorphic appearance and lack of plasmacytic differentiation of this tumor recognized from the early studies. These programs modulated by SOX11 were confirmed to be differentially expressed also in SOX11 positive and negative primary MCL. These results suggest that SOX11 contributes to the development of MCL by blocking the terminal B-cell differentiation program and may influence the aggressive behavior of the tumors by modulating different gene pathways (Vegliante MC et al Blood 2013).

**References**


Orchard J, Garand R, Davis Z et al. A subset of t(11;14) lymphoma with mantle cell features displays mutated IgVH genes and includes patients with good prognosis, nonnodal disease. Blood. 2003;101:4975-4981


Salaverria I, Royo C, Carvajal-Cuenca A, et al CCND2 rearrangements are the most frequent genetic events in Cyclin D1-negative mantle cell lymphoma.

