The cellular origin of mantle cell lymphoma

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Abstract

Mantle cell lymphoma accounts for 5–10% of all non-Hodgkin’s lymphomas and it has one the worst prognosis among all lymphomas. There is no therapy that can be considered as standard. Mantle cell lymphoma can show different “architectural” patterns as well different morphologic variants. Mantle cell lymphoma is believed to derive from marginal zone or peripheral blood memory B-cells. The immunophenotype of the neoplastic cells reflect the phenotype of a mature B-cell, even if mantle cell lymphoma cells are typically CD5+ and CD23−. Mantle cell lymphoma is characterized by the deregulated expression of cyclins D, mainly of cyclin D1, which is targeted by the t(11;14)(q13;q32) chromosomal translocation, the genetic hallmark of the disease. In this review will summarize the main morphologic and immunophenotypic features of the neoplastic cells, and the genetics and biology underlying the disease.

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Cell facts

- Mantle cell lymphoma (MCL) is a lymphoid tumor believed to derive from marginal zone or peripheral blood memory B-cells.
- MCL is characterized by a deregulated expression of cyclins D, mainly of cyclin D1 which is constitutively expressed due to the juxtaposition of the gene to the immunoglobulin heavy chain genes promoter region in the t(11;14)(q13;q32) chromosomal translocation.
- MCL shows a heavy deregulation of the cell cycle and activation of PI3K/AKT, mTOR and NF-kB pathways, possibly offering therapeutic targets to improve patients’ outcome.
- MCL has a very poor prognosis.

Keywords: CCND1; Immunoglobulin; Somatic hypermutation; Chromosomal translocation; NFKB; mTOR

1. Introduction

Mantle cell lymphoma (MCL) accounts for 5–10% of all non-Hodgkin’s lymphomas.

The term MCL represents a group of lymphoma subtypes previously classified as centrocytic lymphoma, lymphocytic lymphoma of intermediate differentiation,
intermediate cell lymphoma or diffuse small-cleaved cell lymphoma (Swerdlow et al., 2001). Despite being previously considered a low-grade and indolent lymphoma, MCL is now considered an aggressive lymphoma. MCL patients have a median age of over 60 years, a male predominance, and they usually have disseminated disease at diagnosis. MCL has one of the worst prognoses among lymphomas, with a median survival of approximately 3 years, with only a few long-survivors. There is no therapy that can be considered as standard (Fisher, 2005; Lenz, Dreyling, & Hiddemann, 2006; Witzig, 2005).

Histologically there are three different “architectural” patterns, which might represent different stages of MCL evolution (Table 1).

The classic MCL can be described as a neoplasm characterized by a monotonous proliferation of small- to medium-sized lymphocytes, with irregular nuclei, condensed chromatin, inconspicuous nucleoli and scant, pale cytoplasm (Swerdlow et al., 2001; Weisenburger & Armitage, 2000) (Fig. 1A). Mitotic figures, although usually not prominent, may be recognizable. Non-neoplastic cells (i.e., macrophages with pink cytoplasm and T-lymphocytes) are interspersed among tumor cells; the amount of T-cells is lower than what observed in follicular lymphomas. There is a loose, enlarged network of follicular dendritic cells. Hyalinized small sized blood vessels such as capillaries is a characteristic finding for MCL.

Besides the classic cytological type, other MCL variants are recognized (Table 2). Among the latter, the blastoid variant (i.e., blastoid, classic subtype) is the most common and it is characterized by medium-sized elements with more dispersed chromatin, appreciable nucleolus and more abundant cytoplasm while, in the blastoid, pleomorphic subtype, cells are large with prominent nucleous/i (Fig. 1B). The proliferation index, measured as mitotic index or as fraction of Ki67+ cells, is presently regarded as the most important prognostic factor for MCL, irrespectively of the morphologic variants, in contrast to the potential prognostic significance of morphologic and architectural variants, which is not well defined (Lenz et al., 2006).

The immunophenotype of MCL cells reflects a mature B-cell arrangement (CD45+, CD19+, CD20+, CD22+, CD24+, CD79a+) with moderate to strong IgM and/or IgD surface immunoglobulins (Weisenburger & Armitage, 2000). Approximately 20% of the cases co-express surface IgG together with IgM, supporting the notion that MCL cells can still undergo immunoglobulin isotype class switch. MCL cells express lambda more commonly than kappa Ig light chains. Similarly to chronic lymphocytic leukaemias (CLL), MCL are usually CD5+ and CD43+, but CD23− (on the converse, CLL are more often CD23+), as well as CD10−. Importantly, CD23 expression is variable in both diseases and, by itself, it cannot be used to make the differen-

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### Table 1

<table>
<thead>
<tr>
<th>Possible histological growth patterns of mantle cell lymphoma</th>
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<tbody>
<tr>
<td><strong>Mantle zone pattern</strong></td>
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<tr>
<td><strong>Nodular pattern</strong></td>
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<td><strong>Diffuse pattern</strong></td>
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Table 2
Variants of mantle cell lymphoma based upon the cytology

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<table>
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<tr>
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<tr>
<td><strong>Classic</strong></td>
<td>Small- to medium-sized lymphoid cells with slightly to markedly</td>
</tr>
<tr>
<td></td>
<td>irregular nuclei, resembling centrocytes</td>
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<tr>
<td></td>
<td>Moderately dispersed chromatin, inconsiderable nucleoli</td>
</tr>
<tr>
<td></td>
<td>Scanty pale cytoplasm</td>
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<tr>
<td></td>
<td>Monotonous cell populations</td>
</tr>
<tr>
<td></td>
<td>Infrequent larger neoplastic cells</td>
</tr>
<tr>
<td></td>
<td>Mitotic figures usually recognizable</td>
</tr>
<tr>
<td><strong>Small cell</strong></td>
<td>Small round lymphocytes, resembling chronic lymphocytic</td>
</tr>
<tr>
<td></td>
<td>leukemia/small lymphocytic lymphoma cells</td>
</tr>
<tr>
<td></td>
<td>Dense, clumped chromatin</td>
</tr>
<tr>
<td><strong>Blastic (blastoid)</strong></td>
<td>Intermediate-sized blasts, with a morphology between a centrocyte</td>
</tr>
<tr>
<td></td>
<td>and a centroblast, and mimicking a lymphoblastic</td>
</tr>
<tr>
<td></td>
<td>lymphoma/acute lymphoblastic leukemia</td>
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<tr>
<td></td>
<td>Fine dispersed chromatin with appreciable nucleoli</td>
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<td></td>
<td>Small cytoplasmic rim</td>
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<tr>
<td></td>
<td>High mitotic index, frequent 'apoptotic bodies'</td>
</tr>
<tr>
<td><strong>Pleomorphic</strong></td>
<td>Medium-to-large cells with large cleaved or oval nuclei</td>
</tr>
<tr>
<td></td>
<td>Clumped or pale chromatin; prominent nucleoli</td>
</tr>
<tr>
<td></td>
<td>Moderate amount of pale cytoplasm</td>
</tr>
</tbody>
</table>

# = as proposed by the European MCL Network (Tiemann et al., 2005).

a “Blastoid, classic variant” in the WHO classification (Swerdlow et al., 2001).

b “Blastoid, pleomorphic variant” in the WHO classification (Swerdlow et al., 2001).

2. Cell of origin

After interaction with the antigen specific for their immunoglobulins, B cells have three possibilities. They can undergo a rapid proliferation and clonal expansion resulting in short-lived plasma cells. They can undergo a T-cell-dependent follicular response with creation of a germinatal centre reaction: moving from the mantle zone, the B-cells heavily proliferate and clonally expand in the dark zone (centroblasts), they move to the light zone where they are selected for antigen binding capacity (centrocytes), and then eventually become memory B-cells or long-lived plasma cells. A third possibility is that B-cells undergo maturation via an extra-follicular, usually T-cell independent, reaction in secondary lymphoid tissue, such as the splenic marginal zone.

By looking at the somatic mutation pattern of the Ig gene rearrangements expressed by lymphoma cells, normal B cell counterparts have been hypothesized for individual lymphoma subtypes. Inside the dark zone, B-cells undergo somatic hypermutation within the Variable (V) regions. Within the light zone, B-cells undergo isotype class switch. The accumulation of somatic mutations within IgH chain and Ig light (IgL) chain V genes greatly increases the affinity of antibodies for antigens.

MCL shows mutated IgH genes in approximately one quarter of the cases, with rates of mutations lower than those observed, for example, in follicular lymphomas, which clearly derive from germinal center B cells. It has been hypothesized that at least a subset of MCL may originate from marginal zone or peripheral blood memory B-cells which have undergone an extra-follicular T-independent antigen response or which bear antigen-independent mutated IgH (Walsh & Rosenquist, 2005), and not from pre-germinatal center B-cells of the mantle zone, as previously believed (Fig. 2).

Differently from CLL, unmutated MCL cases do not clearly show a worse outcome that mutated cases, even if there are papers questioning this issue.

MCL cells show a biased usage of VH genes, VH3-21 being the most common followed by VH3-23, VH3-07 and VH4-34. Cases bearing a rearrangement involving the VH3-21 are usually unmutated, co-express a light chain containing the V\(\lambda\)3-19, and are associated with a better prognosis. On the converse, in CLL VH3-21 positive cases have a worse survival and are usually mutated.

3. Functions and pathogenesis

The t(11;14)(q13;q32) is the genetic hallmark of MCL (Bertoni, Zucca, & Cotter, 2004; Swerdlow et al., 2001). The translocation determines the ectopic and...
Fig. 2. The late maturation process of B-cells with the possible cells of origin of mantle cell lymphoma cell. (A) Lymphoid follicle architecture in the spleen: large cells resident within the germinal centre (GC) are surrounded by a narrow rim of small-to-intermediate cells forming the mantle zone (MZ); this structure is surrounded by a thick ring of intermediate-sized cells with relatively abundant, pale cytoplasm constituting the marginal zone (marginal) (Hematoxylin & Eosin, 200×). (B) Last stages of B-cell maturation in three anatomical compartments (lymphoid follicle, splenic marginal zone, peripheral blood/marginal zone). Black arrows indicate the maturation steps. Red arrows identify the four possible normal B-cell counterparts of mantle cell lymphoma cells (MCL). In the follicle, green represents the mantle zone of a secondary lymphoid follicle; black represents the germinal centre dark zone where clonal expansion and somatic hypermutation occur in centroblasts; grey represents the light zone, where centrocytes undergo antigen-binding selection.

deregulated expression of cyclin D1 (CCND1), due to the juxtaposition of the gene to the strong B-cell immunoglobulin heavy (IgH) chain genes transcription enhancers. The D-type cyclins, in combination with cyclin-dependent kinase 4 and 6 (CDK4 and CDK6) regulate the cell cycle transition between the G1 to the S phase, phosphorylating the retinoblastoma protein, a passage critical to irreversibly commit the cell to complete the cycle. Fluorescence in situ hybridization (FISH) is the technique of choice to demonstrate...
the presence of the translocation. Immunohistochemistry success in determining cyclin D1 over-expression could be hampered by the quality of available material. Polymerase chain reaction (PCR) with primers directed to the breakpoint regions on 11q13 and 14q32 has a high false negative rate (40–60%), although, when positive, it represents an excellent marker for molecular follow-up studies.

Despite the nearly ubiquitous presence of the t(11;14) translocation in MCL, a small percentage of MCL cases do not carry over-express CCND1 and lack any translocation affecting the 11q13 locus (Fu et al., 2005). Six cases of CCND1-negative cases of MCL have been extensively studied (Fu et al., 2005; Salaverria et al., 2007). Despite the absence of CCND1, all the cases expressed the same gene expression signature which distinguishes CCND1-positive MCL cases from other B-cell lymphomas and, clinically, behaved not differently from CCND1-positive cases. CCND1 was apparently replaced by CCND2 in two and CCND3 in four cases. The CCND2 and CCND3 over-expression could be due to epigenetic mechanisms (Fu et al., 2005). The existence CCND1-positive, or CCND2-positive or CCND3-positive MCL cases is reminiscent of what happens in multiple myeloma, the only other B-cell lymphoid neoplasm clearly associated with the presence of a t(11;14)(q13;q32). However, since CCND1-negative cases represent much less than 10% of all MCL patients, a negative FISH result for the t(11;14) in a patient with negative cyclin D1 immunohistochemistry should presently still be considered as a strong data against the diagnosis of MCL.

CCND1 gene gives origin to different transcripts. Two variants raise from an alternative splicing affecting exon 4, which determines CCND1a, a 4.5 Kb long variant, and CCND1b, a 1.7 Kb long form (Marzec et al., 2006; Rosenwald et al., 2003; Wiestner et al., 2007). The latter has a shorter 3′ untranslated region (UTR), is associated with higher protein expression, due to an increased RNA stability, and, clinically, it determines a worse survival than the longer variant (Rosenwald, 2003 #2106; Wiestner, 2007 #4069). It has been very recently shown that the shorter variant can be due to the presence of point mutations, which create new polyadenylation sites, and to genomic deletions targeting the 3′ UTR region (Wiestner et al., 2007).

Besides the t(11;14) translocation, a series of additional recurring transforming events take place. Recurrent DNA gains affect the long arm of chromosomes 3 and 18, while losses frequently target the short arms of chromosome 1, 9 and the long arms of chromosome 9, 6 and 11 (Bertoni, Rinaldi, Zucca, & Cavalli, 2006; Rinaldi et al., 2006; Salaverria et al., 2007): the presence of three or more alteration, gains of 3q27–qter, losses of 8p21-ter, 9p21-ter and losses 9q21–q32 seem to determine a poor clinical outcome (Salaverria et al., 2007).

Many of the genomic aberrations further contribute to the cell cycle deregulation driven by cyclins D expression, with an increased G1/S transition. CDKN1B levels are decreased both for protein sequestration by CCND1/CDK complexes and by increased proteasome-mediated degradation, leading to an increased activity of the Cyclin E/CDK2 complex. A large fraction of cases have inactivation of CDKN2A, often due to a 9p21 genomic deletion. A reduced CDKN2A levels induces an increased activity of the Cyclin D/CDK4–6 complex. Alternatively, cases with normal CDKN2A have amplifications of PCGF4 (BIM1), at 10p11.23, a polycomb transcriptional repressor of CDKN2A. CDK4 levels can also be increased by a 12q13 amplification. MCL can also have inactivation of the gene coding for the retinoblastoma protein by somatic mutations and or genomic/deletions (Pinyol et al., 2007). The 9p21 deletion also causes the loss of ARF, a protein that protects TP53 from MDM2-mediated proteasome degradation (Rosenwald et al., 2003). TP53 degradation can also occur due to increased levels of MDM2, and TP53 can be lost by somatic events occurring at the 17p13 locus. Another mechanism of TP53 inactivation, relevant in MCL, is via loss of the ATM-mediated response to DNA damage. Indeed, the ATM locus, 11q22.3, is frequently deleted in MCL, and the loss of ATM is matched with a higher chromosomal instability (Camacho et al., 2002) and with a particular gene expression signature (Greiner et al., 2006).

The relevance for MCL of the cell cycle deregulation is also highlighted by the impact of gene expression on clinical outcome. A proliferation gene expression signature, composed of 20 genes normally expressed at higher levels in dividing cells than in quiescent cells, identifies groups of patients with different clinical outcome (Rosenwald et al., 2003). Patients with a low proliferation signature have a better outcome than patients with a high proliferation expression signature: 3.6 years versus 1.4 median overall survival (Salaverria et al., 2007). The addition of information on the presence of genomic aberrations (gain of 3q27 and loss of 9q21–q32) to the proliferation gene expression signature seems to further increase the ability to predict the clinical outcome (Salaverria et al., 2007).

The cell cycle is not the only cellular pathway to be altered in MCL. As in many solid and hematological cancers, NF-κB, PI3K/AKT and mTOR pathways are active in MCL (Peponi et al., 2006; Rudelius et al., 2006).
is likely that different mechanisms contribute to these phenomena. One of these might be represented by a constitutive activation of components of the B-cell receptor (BCR) pathway, such as the tyrosine kinase Syk, which has been recently reported to play an important role in B-cell lymphomas, including MCL (Chen, Juszczynski, Takeyama, Aguiar, & Shipp, 2006; Leseux et al., 2006; Rinaldi et al., 2006).

The heavy deregulation of the cell cycle and the activation of the above-mentioned pathways offer a number of possible therapeutic targets that are being explored both in the preclinical and in the clinical setting (Fisher et al., 2006; Kouroukis et al., 2003; Lacrima et al., 2005; Leseux et al., 2006; Marce et al., 2006; Park, Reddy, Reddy, & Groopman, 2007; Rinaldi et al., 2006; Witzig et al., 2005; Yee et al., 2006).

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References


