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REVIEW **Open Access**

The pathologic diagnosis of mantle cell lymphoma

Shaoying Li, Jie Xu and M. James You

Department of Hematopathology, the University of Texas MD Anderson Cancer Center, Houston, TX, USA

Summary. Mantle cell lymphoma (MCL) is a mature B-cell non-Hodgkin lymphoma usually characterized by t(11;14) (q13;q32), or *CCND1* translocation and Cyclin D1 over expression. A very small subset of MCL may lack the t(11;14) (q13;q32) translocation and Cyclin D1 over expression, but show alternative translocations involving *CCND2* and *CCND3*, and over expression of SOX11. In general, MCL has been considered a very aggressive and incurable lymphoma and patients with MCL usually have a poor prognosis. However, indolent variants, including *in situ* mantle cell neoplasm and the recently recognized leukemic non-nodal MCL do exist. In recent years, genome-wide molecular genetic studies have revealed a characteristic MCL genetic profile. This review will focus on the pathologic diagnosis of MCL using the traditional morphological and immunophenotypic strategies combined with cytogenetic characteristics and recently identified molecular profile. Morphological subtypes, immunophenotypic variants, recently recognized indolent variants, as well as MCL risk stratification will also be discussed.

Key words: Mantle cell lymphoma, CyclinD1, *CCND1*, SOX11

Introduction

In the 2017 WHO classification, MCL is defined as a mature B-cell lymphoma usually composed of small to medium sized lymphoma cells with irregular nuclei. The lymphoma cells are monomorphic with the absence of centroblasts, paraimmunoblasts, and proliferation centers (Swerdlow et al., 2017). Immunophenotypically, the lymphoma cells express common B cell markers, CD5 and Cyclin D1, and lack the expression of CD23 and CD200 (Swerdlow et al., 2016a). The genetic hallmark of MCL is *CCND1* translocation with immunoglobulin heavy chain, *IGH*, resulting in the over expression of Cyclin D1. Cyclin D1 plays a very important role in the pathogenesis of MCL. Historically, MCL has been considered as an aggressive B cell lymphoma, although indolent variants of MCL have been well studied and recognized in recent years, including the leukemic non-nodal MCL and *in situ* mantle cell neoplasia (Fernandez et al., 2010; Hsi and Martin, 2014). Despite the rapid progress in treatment regimens, patients with MCL are still incurable. The rapid progress in the field of molecular cytogenetics of lymphomas has been improving our understanding of the molecular pathogenesis of MCL, which has and will lead to the implementation of more effective and targeted therapeutic approaches that may overcome the resistance and make this incurable lymphoma curable at certain point. However, treatment is not within the scope of this chapter, and therefore is not discussed.

Clinical features

MCL is a distinctive subtype of B-cell lymphoma which represents 3% to 10% of all non-Hodgkin lymphoma, in part depends on the geographic regions (Swerdlow et al., 2017). It usually occurs in older males with a median age of about 60 years (range of 29-85 years), and a male to female ratio of ≥2:1(1997).

Patients with MCL can have variable clinical presentations. Some patients present with asymptomatic clonal lymphocytosis detected by peripheral blood flow cytometry, some with nodal or extranodal disease with minimal symptoms, while the majority of patients present with cytopenia and high stage (stage III or IV) disease, extensive lymphadenopathy, hepatosplenomegaly, and/or bone marrow involvement. Lymph nodes are the most common sites of disease, and bone marrow, peripheral blood and spleen are often involved. Other frequently involved extranodal sites include but not limited to the gastrointestinal tract, Waldeyer's ring, lung, kidney, and pleura. A distinctive gastrointestinal presentation of MCL is multiple intestinal polyps, the so-called "lymphomatous polyposis", although it is not specific for MCL (Romaguera et al. 2003). Involvement of the central nervous system may occur, but usually at the time of relapse (Cheah and Seymour, 2013; Cheah et al., 2013).

The diverse presentation of MCL results in variable

Corresponding Author: Shaoying Li, MD, Department of Hematopathology, MD Anderson Cancer Center, 1515 Holcombe Blvd, Unit 72, Houston, TX 77030, USA. e-mail: sli6@mdanderson.org

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clinical courses and may need different treatment strategies. A subset of MCL patients also have disease progression from more indolent form to aggressive forms.

Morphological features

MCL is highly heterogeneous in every aspect, including the morphological features.

Histological patterns

There are 3 architectural patterns in MCL, especially in lymph nodes: mantle zone (mzMCL), nodular and diffuse patterns (Figs. 1, 3). In the mantle zone pattern, the normal nodal architecture is usually preserved, and the lymphoma cells proliferate and expand the mantle zone of the follicles and demonstrate a thick neoplastic mantle zone band surrounding a reactive germinal center (Majlis et al., 1997). In the nodular pattern, the tumor cells infiltrate and colonize the primary and secondary follicles, giving it a nodular or follicular pattern of proliferation, and mimicking follicular lymphoma. The diffuse pattern is the most common pattern; with lymphoma cells diffusely infiltrating the lymph node or extranodal tissue, although focal residual reactive follicles with germinal centers maybe present in some cases. In a subset of cases, two or three patterns may be present and a transition between nodular and diffuse patterns is common.

Cytological variants

MCL has not only different architectural patterns, but also 5 cytological variants that are recognized in the 2017 WHO classification (Swerdlow et al., 2017):

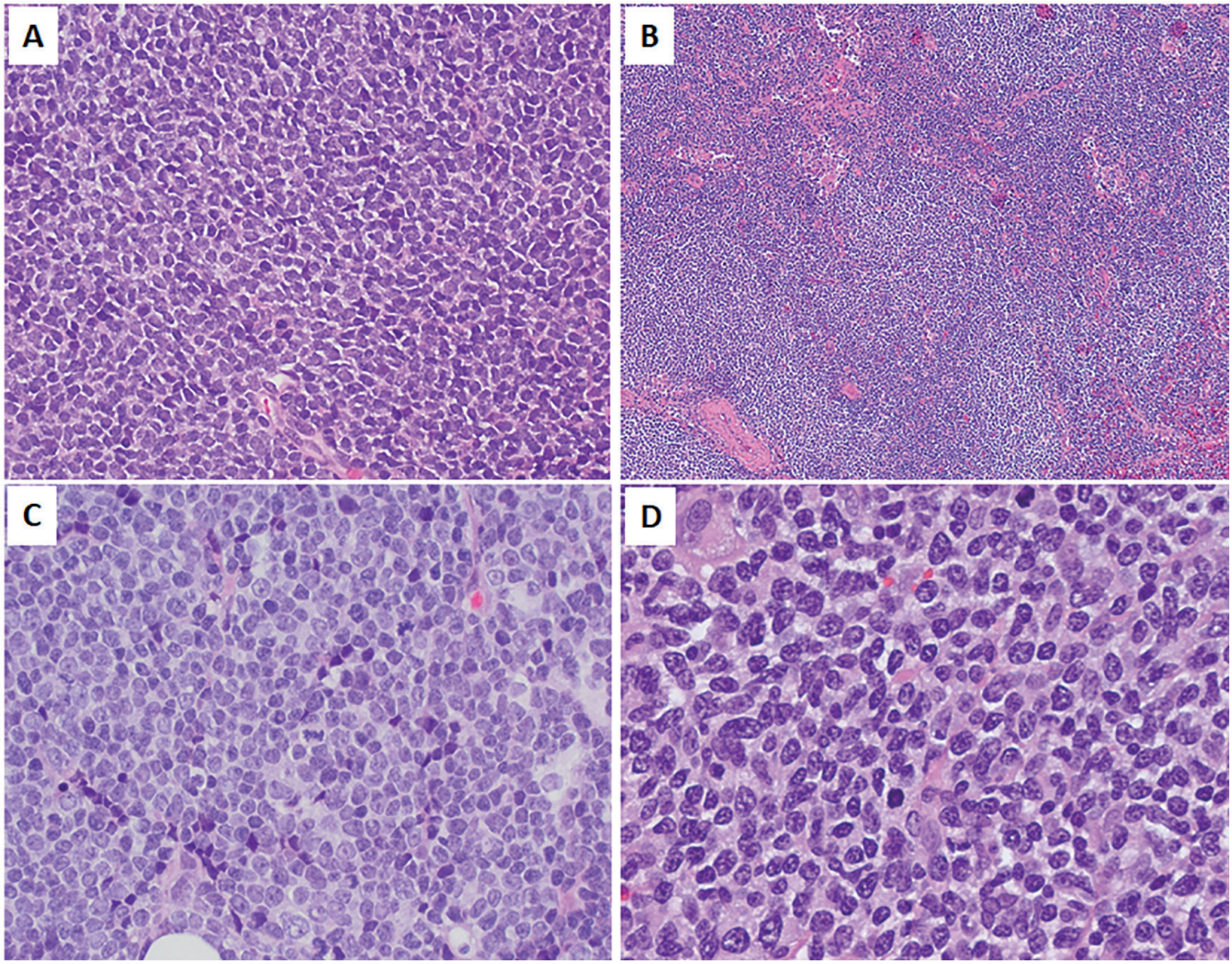

Fig. 1. Morphological patterns and variants of MCL (H&E). **A.** Classic MCL with diffuse pattern. **B.** Monocytoid variant with nodular pattern. **C.** Blastoid variant. **D.** Pleomorphic variant. A, C, D, x 400; B, x 100.

classic or typical MCL; aggressive variants, including blastoid and pleomorphic variants; and other variants, including small- cell and marginal zone-like variants.

The most common cytological type is the classic or typical MCL, which is characterized by a monomorphic lymphoid proliferation of small to medium size lymphoma cells. The lymphoma cells have irregular nuclear contour, condensed but somewhat dispersed chromatin, inconspicuous nucleoli, and scant cytoplasm, resembling centrocytes (Fig. 1A). Large cells with cytological features similar to centroblasts, immunoblasts, or paraimmunoblasts or obvious proliferation centers are absent. Scattered pink or eosinophilic epithelioid histiocytes are often present, as are small vessels with hyalinized vessel walls. Therefore, monomorphic small to medium sized tumor cells, pink epithelioid histiocytes, and hyalinized vessels are often been considered as the morphological diagnostic triad for MCL.

In the small cell variant of MCL, the lymphoma cells are monomorphic small lymphocytes with round nuclei, condensed chromatin, and scant cytoplasm, similar to classical chronic lymphocytic leukemia or small lymphocytic lymphoma (CLL/SLL) cells. However, medium to larger cells such as prolymphocytes, paraimmunoblasts, and proliferation centers are not present. This small cell variant mostly occurs in the leukemic non-nodal subtype of MCL (Fernandez et al., 2010). of, and In the marginal zone-like MCLvariant, the lymphoma cells are monocytoid B cells with abundant pale cytoplasm (Fig. 1B), which is a great mimicker of marginal zone lymphoma.

Compared to the classic MCL and the above mentioned two cytological variants, blastoid and pleomorphic variants are clinically more aggressive. In the blastoid variant (Fig. 1C), the tumor cells are medium in size, with slightly irregular rounded nuclei, dispersed fine chromatin, inconspicuous to conspicuous nucleoli, and scant cytoplasm, resembling the blasts in lymphoblastic lymphoma/leukemia. In the pleomorphic variant (Fig. 1D), as the name suggests, the lymphoma cells are large and pleomorphic with irregular round or cleaved nuclei, finely dispersed chromatin and conspicuous nucleoli, similar to diffuse large B cell lymphoma (DLBCL) cells (Ott et al., 1994). Some blastoid variant MCL cases may exhibit both the classic type, and blastoid or pleomorphic variants in different areas in the same tumor. In such cases, a previous study recommended reporting both cytological features but classifying them into the more aggressive blastoid or pleomorphic variants (Aukema et al., 2018). These two aggressive variants typically have a diffuse growth pattern, only occasionally show a nodular or mantle zone pattern (Dreyling et al., 2018).

In addition, plasma cell infiltration has been identified in some MCL, including either polytypic or monotypic plasma cell infiltration. Rare cases of MCL with plasmacytic differentiation have been reported, in which the plasma cell component may or may not be clonally related to the lymphoma cells (Visco et al., 2011; Ribera-Cortada et al., 2015; Swerdlow et al., 2016b). The lymphoma cells in such cases are often Cyclin D1 positive but SOX11 negative, and these patients usually had an indolent clinical process.

Low-grade B cell lymphoma can transform into a more aggressive DLBCL. Similarly classical MCL and the small cell or marginal zone variants can transform into the more aggressive blastoid or pleomorphic variants, usually at relapse. On the contrary, MCL that presents as blastoid or pleomorphic morphologies at diagnosis may also relapse as classical MCL morphology or any other more indolent morphology (Vogt et al., 2013).

Organ specific morphological features

Most patients with MCL present with advanced stage disseminated disease with frequent extranodal involvement including bone marrow, peripheral blood, spleen, gastrointestinal tract, and others.

Bone marrow infiltration is present in 50% to 90% of MCL cases (Pittaluga et al., 1996; Saksena et al., 2019) and tumor load ranges from <5% up to >90%. The lymphoma infiltration pattern includes a nodular or interstitial lymphoid aggregates, interstitial, or diffuse infiltration, or a combination of any of them (Cohen et al., 1998). Peripheral blood involvement by MCL is common. Although morphological review of peripheral blood smear may be indicative of MCL involvement in the majority of such MCL cases, virtually all of such cases need flow cytometry immunophenotypic confirmation, especially in a small subset with no overt tissue involvement (Ferrer et al., 2007). The cytological features and spectrum are the same as observed in solid tissue sections, except that the chromatin is usually more open and the nucleoli is more prominent, even in the typical type.

Splenic involvement by MCL is also common and usually characterized by a nodular pattern in the white pulp with variable degree of red pulp infiltration, which highly resemble splenic marginal zone lymphoma. Cytologically, splenic MCL is similar to the cases that occur in other tissue sections. In some splenic MCL cases, they also mimic splenic marginal zone lymphoma, with lymphoma cells in the center of the nodules showing a typical mantle cell cytology, while those in the periphery have abundant pale cytoplasm, giving the lymphoma cells a monocytoid appearance (Piris et al., 1998).

Immunophenotype

MCL is a mature B cell non-Hodgkin lymphoma, and therefore strongly expresses pan-B cell markers, including CD19, CD20, CD22, PAX5, CD79a. In addition, MCL usually expresses cell surface immunoglobulin IgM and IgD and one of immunoglobulin light chains, with lambda light chain

being more frequent than kappa light chain. The characteristic immunophenotype of MCL is co-expression of the pan-T cell marker CD5 and Cyclin D1, but without expression of CD10, CD23, CD200, BCL6 and LEF1 (Fig. 2). MCL lymphoma cells are generally positive for CD43, BCL2, SOX11, and FMC7 (Swerdlow et al., 2017). MYC is only expressed in a very low number of cells in most typical type of MCL cases, but may show overexpression (≥40%) in a subset of cases, especially those with *MYC* rearrangement, frequently in the blastoid variant (Oberley et al., 2013; Wang et al., 2020). TP53 over expression presents in approximately 30% of cases of MCL, which is more often seen in blastoid and pleomorphic variants (Hernandez et al., 1996; Aukema et al., 2018; Wang et al., 2020).

A small subset of MCL show an atypical immunophenotype, including the absence of CD5 or SOX11 expression, or the presence of CD10, CD23, or CD200 expression. Among them, CD23 expression is the most common atypical phenotype, and presents in up to 45% of MCL. However, the largest study so far showed a 13% CD23-expression cases (Schlette et al., 2003; Kelemen et al., 2008; Saksena et al., 2019). CD23 expression in MCL is often dim and partial, unlike the moderate to strong positivity often seen in CLL/SLL. CD23 expression correlates with a higher frequency of CD200 expression, lower frequency of SOX11 expression, and a higher frequency of leukemic non-nodal presentation. Lack of CD5 expression has been reported in 5-10% of MCL (Puente et al., 2018; Miao et al., 2019). CD10 and BCL6, two markers that define

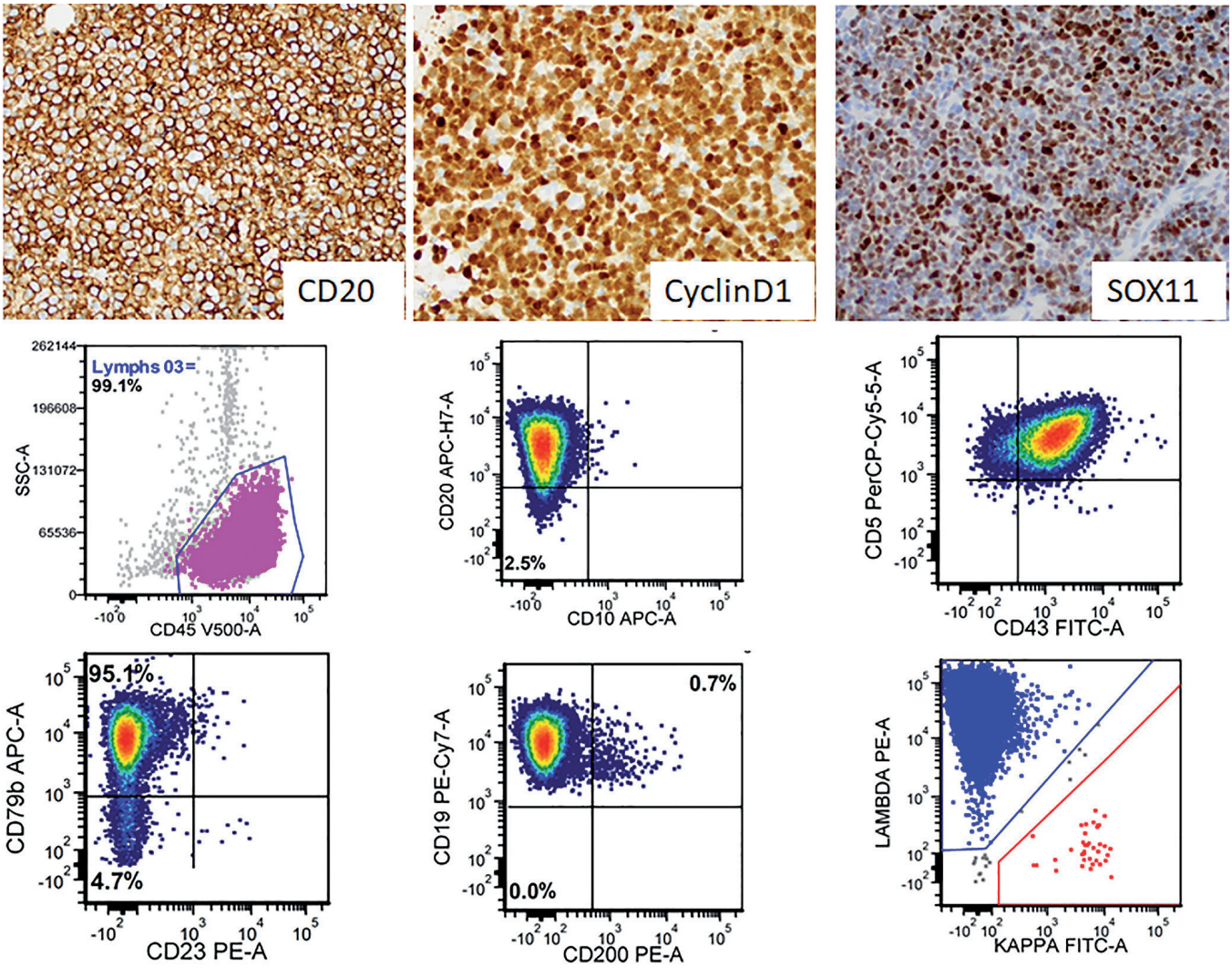

Fig. 2. Characteristic immunophenotype of MCL. MCL expressing CD5, CD19, CD20, CD79a, Cyclin D1, and SOX11, and negative for CD10, CD23, CD200 and LEF1 (not shown). Most of MCL cases demonstrate surface light chain restriction, with lambda more often than kappa light chain (Upper panel: immunohistochemistry for CD20, CyclinD1, and SOX11, 400X; Middle and lower panels: flow cytometry).

germinal center origin, are also expressed in a small number of MCL cases, more frequently in blastoid or pleomorphic variants than in cases with typical morphology (Camacho et al., 2004; Akhter et al., 2015; Pizzi et al., 2017; Xu et al., 2018). CD200, a marker generally used to differentiate MCL from CLL/SLL, is usually absent in MCL and only expressed in occasional cases, especially in leukemic non-nodal cases (Hu et al., 2018; Saksena et al., 2019).

Cyclin D1

Cyclin D1 expression is the immunophenotypic hallmark of MCL and is very useful for diagnosis (Fig. 2). CyclinD1 over expression is mainly due to the underlying *CCND1/IGH* translocation, which is present in approximately 95% of MCL (Vasef et al., 1997). Therefore, around 5% of MCL is Cyclin D1-negative, which will be discussed in detail in a later section. However, not all Cyclin D1 negative MCLs lack *CCND1* rearrangement. Rare MCL with the *CCND1/IGH* may show no Cyclin D1 expression due to the underlying mutations at the C-terminal, resulting in the expression of a *CCND1* isoform missing exon 5. Cyclin D1 encoded by this mutant *CCND1* isoform lacks binding sites by conventional antibodies (Iaccarino et al., 2018).

Although CyclinD1 expression is important for the diagnosis of mantle cell lymphoma, it is not 100% specific. Cyclin D1 is also expressed in other lymphomas or hematopoietic neoplasms, including approximately 25% of plasma cell myelomas, a small subset of hairy cell leukemia, some proliferation centers of CLL, ~1% of DLBCL, occasional primary mediastinal large B cell lymphoma, a small number of T cell lymphomas (ALK positive or negative anaplastic large cell lymphoma, and peripheral T cell lymphoma, not otherwise specified), and some histiocytic neoplasms such as Rosai-Dorfman disease and Langerhans histiocytosis (de Boer et al., 1996; Specht et al., 2004; Song et al., 2016; Shanmugam et al., 2017; Baraban et al., 2019; Chen et al., 2019; Garces et al., 2019). Cyclin D1 expression in plasma cell myeloma maybe related to the t(11;14) (q13;q32), or *CCND1* rearrangement, *CCND1* amplifications, or other mechanisms. Expression in all other entities is not due to the *CCND1* rearrangement. However, these tumors usually do not express SOX11, except a subset of hairy cell leukemia with both cyclinD1 and SOX11 expression (Chen et al., 2010; Hsiao et al., 2012; Garces et al., 2019).

SOX11

SOX11 is expressed diffusely and strongly in 70-90% of MCL (Swerdlow et al., 2017; Saksena et al., 2019) (Fig. 2), from *in situ* mantle cell neoplasm to Cyclin D1 negative MCL. Therefore, SOX11 has been recognized as a sensitive and relatively specific marker for the diagnosis of MCL in 2008 (Ek et al., 2008). It is especially useful for the diagnosis of Cyclin D1 negative MCL. SOX11 is virtually negative in normal or reactive lymphoid cells as well as most other mature B or T cell lymphoid neoplasms (Ek et al., 2008; Dictor et al., 2009; Mozos et al., 2009), although the total number of studied cases in each category are still very small. In addition to MCL, SOX11is expressed in up to 50% of Burkitt lymphomas, most immature lymphoid neoplasms, including B and T-lymphoblastic lymphoma/leukemia, some T-prolymphocytic leukemia, and some CyclinD1 positive hairy cell leukemia (Dictor et al., 2009; Mozos et al., 2009; Chen et al., 2010).

Ki67

Ki67 is a marker of cell proliferation, which is associated with tumor aggressiveness. Ki67 proliferative rate is highly variable in MCL. It is usually low (<30%) in classic and small cell variant of MCL, and high in blastoid and pleomorphic variants (Shrestha et al., 2015). However, some classic cases may show a high Ki67 proliferation index (Determann et al., 2008; Klapper et al., 2009). Therefore, the 2017 WHO classification recommends morphological features as the only criteria to define MCL variants. Ki67 proliferation rate has significant prognostic significance, which will be discussed in more detail later.

Genetics and pathogenesis

IG genes are clonally rearranged in MCL, just like in all other B cell lymphomas. In most cases of MCL, *IGHV* is unmutated or minimally mutated. However, *IGHV* somatic hypermutation is present in a small subset of cases.

The t(11;14) (q13;q32), or *CCND1/IGH*, which juxtaposes the immunoglobulin heavy-chain gene in chromosome 14 to a region on 11q13 upstream of *CCND1* is the genetic hallmark of MCL. It is the primary genetic event in the pathogenesis of MCL (Li et al., 1999) and present in ≥95% of MCL cases. This translocation can be detected by fluorescence *in situ* hybridization (FISH) using the traditional *IGH* and *CCND1* dual color dual fusion probes. Occasionally, immunoglobulin light chains also serve as the *CCND1* translocation partner, which can be detected by the *CCND1* break-apart screening probe followed by the confirmative *CCND1* and kappa or lambda fusion probes (Royo et al., 2011).

Rare B cell lymphomas were reported to express strong diffuse Cyclin D1 protein, but showed no *CCND1* rearrangement by FISH using either the fusion or break-apart probes. Interestingly, whole-genome sequencing or FISH using custom bacterial artificial clones-labeled probes have detected that these lymphomas carry cryptic rearrangements of *IGK* or *IGL* enhancers with *CCND1*, which resulted in Cyclin D1 expression (Peterson et al., 2019; Fuster et al., 2020; Polonis et al., 2020). These rare B cell lymphomas showed very similar clinical and pathologic features to MCL, suggesting that they should

be included in the MCL category. The translocation is acquired in precursor B cells mediated by recombination-activating genes in most cases, with only 8% of those cases showing that the translocation occurs in mature B cells mediated by activation-induced cytidine deaminase (Nadeu et al., 2020). The *CCND1* rearrangement results in the overexpression of CyclinD1, or an aberrant transcript which is translated into a CyclinD1 protein with increased half-life. Cyclin D1 is a cell cycle regulatory protein. Constitutively aberrant overexpression of Cyclin D1 activates Cyclin D1 dependent kinase pathway, overcomes the cell cycle suppressive effect of RB and p27, and promotes cell growth and malignant transformation, leading to the development of MCL (Jares et al., 1996; Quintanilla-Martinez et al., 2003).

Although *CCND1* rearrangement is the primary cytogenetic abnormality that defines MCL, it is not sufficient to cause MCL by itself. This has been evidenced by both animal models and the presence of clonal B cells with *CCND1* rearrangement in peripheral blood of healthy persons (Lecluse et al., 2009). Secondary genetic alterations are very common in MCL, presenting in >90% of cases, play important roles along with *CCND1* rearrangement in the pathogenesis of MCL. The secondary cytogenetic changes include gains/amplifications of 3q26 in 31- 51%, 7p21 in 16 - 34%, 8q24 or *MYC* in 16-36% of cases and others; loss of 1p, 2q, 6q, 8p, 9p (*p16 INK4a* and *p14ARF*), 9q, 10p, 11q (*ATM*), 13q, 17p (*TP53*), 19p, and others (Royo et al., 2011; Bea and Amador, 2017). Copy neutral loss of heterogeneity has been detected in up to 60% of cases by SNP studies (Bea et al., 2009; Royo et al., 2011). In addition, tetraploid abnormalities are also frequent changes in the pleomorphic variant. These cytogenetic abnormalities involve genes that participate in multiple signaling pathways in the pathogenesis of MCL, including but not limited to cell cycle regulation (*CCND1, RB*, etc), DNA damage response pathway (*ATM, TP53*, etc), and cell proliferation and apoptosis (*BCL2, MYC*, etc).

Various next-generation sequencing studies have demonstrated a very complex mutational landscape in MCL (Hill et al., 2020). A recent meta-analysis reviewed 32 published genetic mutational studies of MCL and included 2,127 patients. The analysis revealed that *ATM* was the most frequently mutated gene (43.5%), which is followed by the mutations of *TP53* (26.8%), *CDKN2A* (23.9%), and *CCND1* (20.2%), Additionally aberrations in *IGH* (38.4%) and *MYC* (20.8%) were frequent detected by cytogenetic methods. Moreover, other common baseline mutations were detected, including *NSD2* (15.0%), *KMT2A* (8.9%), *S1PR1* (8.6%), and *CARD11* (8.5%). Furthermore, the meta-analysis demonstrated a change in mutational status from baseline at diagnosis to the time at disease progression, with the highest gene mutational frequency difference (>5%) observed in *TP53, ATM, KMT2A, MAP3K14, BTK, TRAF2, CHD2, TLR2, ARID2, RIMS2, NOTCH2, TET2, SPEN, NSD2, CARD11, CCND1, SP140, CDKN2A,* and *S1PR1*. Finally, studies also showed that *MYC* translocation and *TP53* mutation are two key factors often associated with disease progression (Hernandez et al., 1996; Wang et al., 2020).

Recent studies have shown that SOX11 also plays an important oncogenic role in the pathogenesis of MCL. SOX11 expression is also reported in "*in situ*" mantle cell neoplasia, suggesting that SOX11 may play a role in the early stage of the pathogenesis of MCL, similar to *CCND1* (Adam et al., 2012; Carvajal-Cuenca et al., 2012). SOX11 is involved in multiple signaling pathways, including the interference of B-cell differentiation by interacting with PAX5 and BCL6, impacting lymphoma microenvironments, cell cycle promotion, and inhibiting apoptosis (Vegliante et al., 2013; Palomero et al., 2016; Beekman et al., 2018).

All the results in these genetic studies support dividing MCL into two genetic subtypes: conventional type (cMCL) and the leukemia non-nodal subtype (lnnMCL). Both types share a similar global gene expression profile, although they also have some differences. The cMCL is most common and originated from naïve B cells that never enter into germinal center and with no or limited *IGHV* somatic mutation, while the lnnMCL is derived from experienced memory B cells with *IGHV* somatic mutation (Jares et al., 2012; Navarro et al., 2012). cMCL shows SOX11 overexpression, and carries significantly higher numbers of structural variants, copy number alterations, and driver changes than lnnMCL, and is therefore clinically more aggressive (Nadeu et al., 2020). Interestingly, *ATM* mutation is only observed in cMCL. On the contrary, lnnMCL usually lacks SOX11 expression, and has less chromosomal abnormalities and an indolent process. The two subtypes also differ in epigenetic pathways and driver makeups.

Special subtypes

In situ mantle cell neoplasm

In the 2017 WHO classification, *in situ* mantle cell neoplasm (isMCN) is defined by the presence of Cyclin D1 positive lymphoid cells with *CCND1* rearrangement in the mantle zone of otherwise reactive hyperplastic appearing follicles (Swerdlow et al., 2017). It was referred to as *in situ* MCL previously. However, it is rare and usually an incidental finding with very limited malignant potential. Therefore, *in situ* MCL was renamed as isMCN to avoid unnecessary treatment (Carvajal-Cuenca et al., 2012). The cells of isMCN are mainly located in the inner layers of the mantle zone of normal lymphoid follicles, often admixed with Cyclin D1 negative lymphocytes, and there is no expansion of the mantle zone in isMCN (Adam et al., 2012; Carvajal-Cuenca et al., 2012). Occasionally, the cells of isMCN can also be scattered throughout the mantle zone or intrafollicular area. IsMCN can be multifocal, mainly nodal but can also occur in extranodal sites. Although

isMCN can present before, after, or at the same time as overt MCL or other lymphomas, only rare isMCN cases progress to overt MCL. In previous studies, no isMCN were found in 100 hyperplastic lymph nodes in one study, and only one of the 12 cases progressed to overt MCL with a long latency period in another study (Adam et al., 2012; Carvajal-Cuenca et al., 2012). Some isMCN express SOX11 while others do not, suggesting that the isMCN may be a common precursor lesion for both the SOX11 positive and SOX11 negative MCL (Carvajal-Cuenca et al., 2012). IsMCN needs to be differentiated from MCL with a mantle zone growth pattern. The former does not expand the mantle zone, but the latter has a mantle zone densely infiltrated and expanded by Cyclin D1 positive cells that may focally extend to interfollicular regions (Fig. 3). This differential diagnosis has a significant clinical impactas MCL with mantle zone pattern has a high potential to progress to a disseminated disease.

Leukemic non-nodal mantle cell leukemia

The leukemic non-nodal MCL (lnnMCL) is a new special subtype of MCL first recognized by the 2017 WHO classification. It is defined by the presence of MCL only in peripheral blood, bone marrow, and/or spleen, with no or minimal nodal MCL (lymph node <1-2 cm) (Swerdlow et al., 2017). Morphologically, lnnMCL shows more frequent small cell or typical cytology. Leukemic blastoid MCL has medium to large cells with irregularly round nuclei, finely dispersed chromatin, inconspicuous nucleoli, and scant or little cytoplasm. Leukemic pleomorphic MCL has very large lymphoma cells with prominent nucleoli. Immunophenotypically, lnnMCL more frequently expresses CD23 and CD200 but lacks the expression of CD5 and

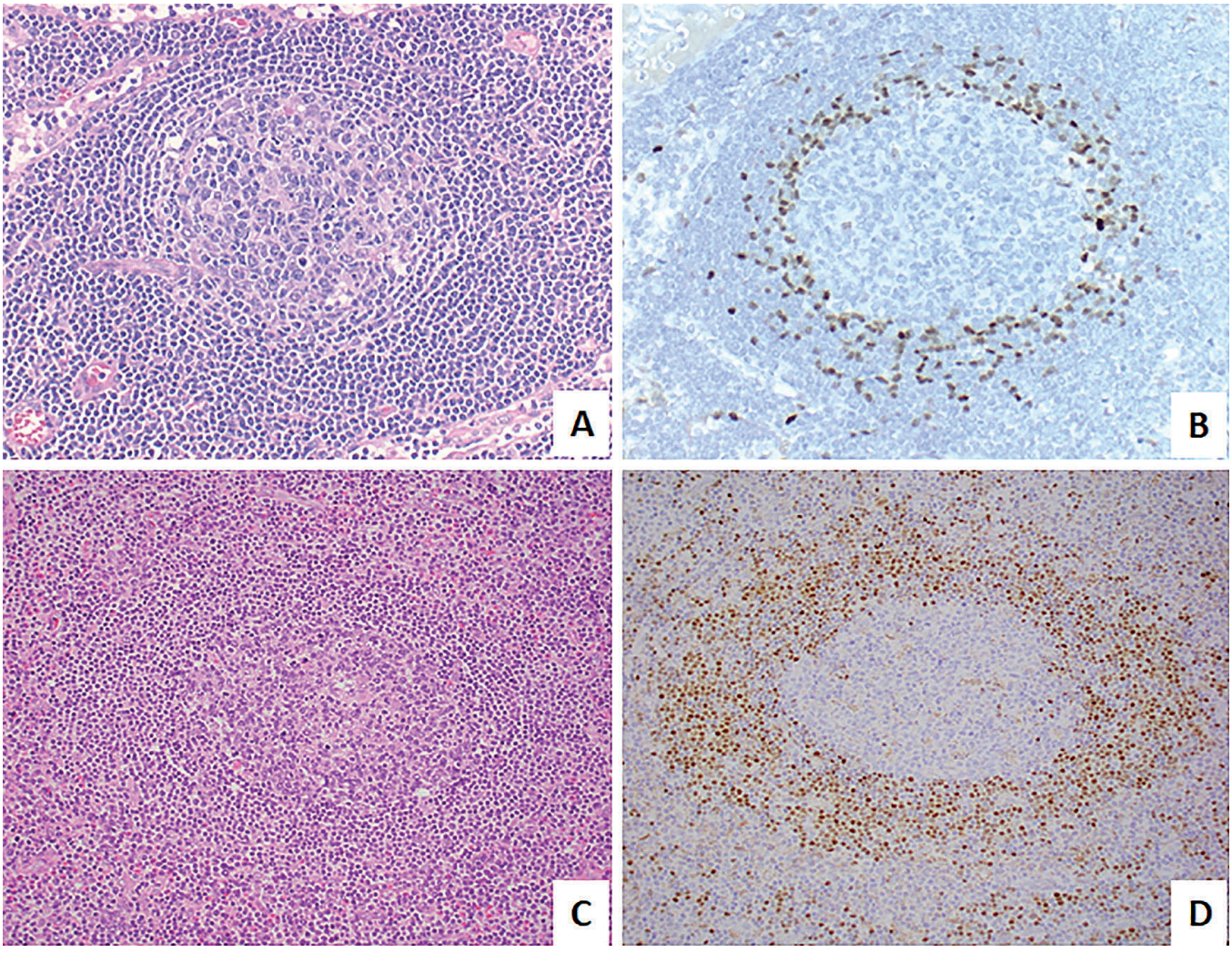

Fig. 3. *In situ* mantle cell neoplasm **(A, B)** and mantle cell lymphoma, mantle zone pattern **(C, D)**. A, C: H&E; B, D: Cyclin D1 immunohistochemistry. x 200.

SOX11 (Hu et al., 2018; Miao et al., 2019; Saksena et al., 2019). Molecular genetic studies showed that lnnMCL has the same global genome expression profile as cMCL, thus, supporting that lnnMCL is a subtype of MCL. Genomic studies also showed that typical MCL carried significantly higher numbers of structural variants, copy number alterations, higher DNA methylation, and driver changes than lnnMCL, with exclusive alterations of ATM in cMCL (Nadeu et al., 2020). In contrast to conventional MCL, most lnnMCL have mutated *IGHV* and simple karyotypes with no or very few additional chromosomal abnormalities except the t(11;14)(q13;q32) (Fernandez et al., 2010; Royo et al., 2012; Swerdlow et al., 2017). Gene expression profiling studies found that lnnMCL lacks tumor invasion properties and angiogenic potential observed in cMCL driven by SOX11 expression (Palomero et al., 2014; Balsas et al., 2017). Based on the above differences, it is easy to understand that lnnMCL has a generally better prognosis than cMCL, shows an indolent clinical course, and does not warrant treatment for a long period (Orchard et al., 2003; Fernandez et al., 2010; Nadeu et al., 2020). However, a subset of these cases may progress to a more aggressive, disseminated nodal and extranodal disease with blastoid or pleomorphic morphology. Additionally acquired cytogenetic aberrations, such as *TP53* mutation, *MYC* rearrangement, and complex karyotype, are the mediators of these progressions (Royo et al., 2012; Wang et al., 2020).

Cyclin D1-negative MCL

Occasional B cell lymphomas show the same morphological and immunophenotypic features as MCL, but lack Cyclin D1 expression and the *CCND1* rearrangement. They also have a global gene expression profile and clinical characteristics similar to Cyclin D1 positive MCL. Therefore, they are considered as a genetic variant of MCL named Cyclin D1-negative MCL (Fu et al., 2005; Salaverria et al., 2007; Zeng et al., 2012). Cyclin D1-negative MCL may have the same morphological variants as Cyclin D1-positive MCL. Cyclin D2 or cyclin D3 are strongly expressed in Cyclin D1-negative MCL, but the expressions of Cyclin D2 and Cyclin D3 are not useful for the diagnosis as the markers are also expressed in other B cell lymphomas. SOX11 staining is a useful marker for the diagnosis of the Cyclin D1-negative MCL (Mozos et al., 2009; Sander et al., 2016). The pathogenesis of CyclinD1-negative MCL is also similar to Cyclin D1-positive MCL. Instead of *CCND1*, most cases of Cyclin D1-negattive MCL harbors *CCND2* or *CCND3* rearrangement, and the partner genes are usually *IG* genes, especially *IG* light chains (Salaverria et al., 2013). Similar to what occasionally occurs in CyclinD1 positive MCL, some CyclinD1-negative MCL may also carry cryptic insertions of the kappa and lambda enhancer regions adjacent to *CCND2* and *CCND3*, which results in the overexpression of the corresponding mRNAs and proteins (Salaverria et al., 2013; Martin-Garcia et al., 2019). Due to the small size of the enhancer region, these translocations are cryptic by routine FISH testing for *CCND2* or *CCND3*. Their detections rely on specific FISH probes in routine formalin fixed, paraffin embedded tissues or next generation sequencing studies. Interestingly, occasional B cell lymphoma cases show morphological and phenotypic features of MCL with SOX11 expression, but do not express any of these three Cyclin D subtypes. Instead they have up-regulation of CCNE1 and CCNE2 with no overt genetic abnormalities (Martin-Garcia et al., 2019). Therefore, to diagnose most of the CyclinD1-negative MCL cases, a combined strategy is needed, including the study of SOX11 expression by immunohistochemistry, *CCND2*/ *CCND3* rearrangements by FISH using break-apart probes, and next generation sequencing studies.

Diagnosis and differential diagnosis

No single marker or aberration is diagnostic of MCL in all cases, including the presence of *CCND1* rearrangement, which may be identified in approximately 5% of plasma cell myeloma (de Boer et al., 1996). Therefore, the diagnosis of MCL relies on a combined strategy including multiple factors: 1) morphological features; 2) characteristic immunophenotype, including positive stains for CD5, Cyclin D1, and/or SOX11, but absence of CD23 and CD200 expression; 3) presence of t(11;14)(q13;q32) and/or *CCND1* rearrangement. Some MCL cases may be diagnosed with typical morphology, characteristic immunophenotype and clinical features without cytogenetic tests. A small subset of cases may lack CD5 expression, or express one or more of the markers usually not expressed in MCL, such as CD10, CD23 and CD200. In such cases with atypical immunophenotype, typical morphology and Cyclin D1 and SOX11 expressions are sufficient to diagnose MCL. Otherwise, karyotype and/or FISH to demonstrate the presence of *CCND1* rearrangement is recommended, except rare Cyclin D1-negative MCL as detailed in the Cyclin D1-negative MCL section. SOX11 is a useful marker in the differential diagnosis of MCL because it is also expressed in the rare Cyclin D1-negative MCL. The expression of SOX11 in such cases has facilitated its recognition and correct classification.

The differential diagnosis of MCL is broad. It needs to be differentiated with all other small and large B cell lymphomas, which is usually easy based on morphologic and immunophenotypic findings. The main differential diagnosis of MCL is chronic lymphocytic leukemia / small lymphocytic lymphoma (CLL/SLL) as both MCL and CLL/SLL express CD5. But the differential diagnosis between them is usually easy based on characteristically different morphology and immunophenotype. MCL expresses bright CD20 and lacks the expressions of CD23, CD200, and LEF1. In

contrast, CLL/SLL shows CD23, CD200, LEF1 and dim CD20 expression. The definitive differential diagnosis between MCL and all other B cell lymphomas includes Cyclin D1 and/or SOX11 expressions, and *CCND1* rearrangement, as they are present in MCL but do not occur in CLL/SLL or any other mature B cell lymphoma.

mzMCL: Mantle zone pattern of MCL needs to be differentiated from isMCN, Cattleman disease, and reactive mantle cell hyperplasia. The differential diagnosis with isMCN is described in the isMCN section. The feature of mzMCL is the expansion of the mantle zone by Cyclin D1-positive tumor cells. And there is no Cyclin D1 expression in the lymphocytes in either Cattleman disease or reactive mantle cell hyperplasia.

Nodular pattern MCL: When MCL demonstrates a nodular pattern, the differential diagnosis includes mainly follicular lymphoma. In such cases, the immunophenotype helps to establish the correct diagnosis.

Marginal zone-like MCL: In a small number of MCL cases, the lymphoid cells have a monocytoid (abundant pale cytoplasm) cytology, mimicking marginal zone lymphoma. Occasional MCL may have plasmacytic differentiation, a feature often observed in marginal zone lymphoma. The differential diagnosis relies on the immunophenotype and detection of *CCND1* rearrangement.

Blastoid/ pleomorphic MCL: Blastoid MCL shows medium to large cells with high nuclear-to-cytoplasmic ratio, round nuclei, finely dispersed chromatin and inconspicuous nucleoli, mimicking blasts in acute leukemia. When such types of cases are presented in blood and bone marrow, it is very easy to misdiagnose them as acute leukemia. Pleomorphic MCL have variably sized and shaped cells, including very large cells with prominent nucleoli, which may be misinterpreted as DLBCL. When presenting as a leukemic form, the blastoid/ pleomorphic MCL cases may also be confused with acute leukemia. Full immunophenotypic evaluation and cytogenetic and/or molecular studies to detect the presence of the t(11;14)(q13;q32) or *CCND1* rearrangement are the solution for the correct diagnosis of these cases (Schlette et al., 2001).

Currently, molecular tests such as next generation sequencing have not been routinely used in clinical practice in the diagnosis and differential diagnosis of MCL. However, these tests may play a role in the future when they become widely available, especially in some lnnMCL cases. It has been reported that a molecular assay based on the 16-gene expression profile can reliably distinguish classical MCL and lnnMCL using blood samples (Clot et al., 2018).

Prognosis

In general, MCL is considered as an incurable aggressive B cell lymphoma with a median survival of only 3-5 years(Swerdlow et al., 2017). With modern chemotherapy or chemotherapy-free regimens, a subset of patients have shown improved survival. However, the prognosis is still significantly variable and overall poor. Multiple factors have been shown to be associated with prognosis.

Mantle cell lymphoma international prognostic index (MIPI)

The most significant clinical prognostic factor is the MCL International Prognostic Index (MIPI) score. The MIPI includes patient age, ECOG performance status, LDH levels, and white blood cell count. The MIPI divides the patients into low-, intermediate-, and high-risk categories (Hoster et al., 2008). The addition of Ki-67 proliferation index further improves the prognostic value of the above simplified MIPI score, which is referred as the biological MIPI (Hoster et al., 2014).

Subtype and morphological variants

The 2017 WHO classification recognizes two subtypes of mantle cell leukemia, the conventional MCL and the lnnMCL. Both traditional and new genomic studies have shown that the lnnMCL has characteristics distinctly different from the classic MCL. LnnMCL has leukemic but no nodal presentation, lower LDH level, more frequently mutated *IGVH*, and less genomic complexity, and therefore a significantly better overall survival and longer time to first treatment (Clot et al., 2018; Nadeu et al., 2020). Among the morphological variants, blastoid and pleomorphic variants are aggressive variants (Shrestha et al., 2015). However, these variants usually have a high Ki67 proliferation index, high frequency of *MYC* rearrangements and expression, more frequent deletion, mutation, and over-expression of TP53, and a complex karyotype (Hoster et al., 2016; Wang et al., 2020). Therefore, it is unclear if the prognostic significance of these morphological variants is independent of the above factors.

Proliferation rate

The proliferation rate of lymphoma cells is very important for the prognosis of MCL. High proliferation rate is shown by high mitotic rate, and usually measured by the Ki67 proliferation index, with Ki67>30% considered as a worse prognostic factor, independent of morphological variants or subtypes (Katzenberger et al., 2006; Klapper et al., 2009; Hoster et al., 2016; Dreyling et al., 2018). Gene expression profiling studies also identified an expression signature composed of genes related to proliferation that can stratify patients with MCL into different risk groups. Recently this has been validated in a new 35 genes assay (MCL35 assay, including 17 genes associated with proliferation and 18 housekeeping genes) using RNA extracted from formalin

fixed and paraffin embedded tissues and a NanoString platform (Scott et al., 2017). Using this assay, MCL patients can be stratified into 3 risk groups, low, standard, and high-risk groups, with a median survival of 8.6, 2.6, and 1.1 years, respectively. The proliferation signature score of MCL35 assay correlates with the Ki67 proliferation index very well and has even better prediction. The results have been highly reproducible among laboratories and the usefulness of this assay has been confirmed in MCL patients treated in different clinical trials (Holte et al., 2018; Rauert-Wunderlich et al., 2019; Ramsower et al., 2020).

SOX11

SOX11, an important gene associated with the pathogenesis of MCL, is one of the most differentially expressed genes in MCL. It is often expressed in conventional MCL, but not expressed in the majority of the indolent lnnMCL, either at mRNA or protein level (Fernandez et al. 2010). However, the prognostic significance of SOX11 expression is controversial. Some studies reported that SOX11 expression was associated with a poorer prognosis in MCL patients, while others showed no prognostic effect or a better prognosis (Wang et al., 2008; Dreyling et al., 2011; Navarro et al., 2012, Nygren et al., 2012; Nordstrom et al., 2014; Aukema et al., 2018; Xu et al., 2019).

Molecular cytogenetic aberrations

Cytogenetic and genomic studies have shown that complex karyotypes and genomic complexity are associated with an aggressive clinical behavior and a poor prognosis (Greenwell et al., 2018; Nadeu et al., 2020). Individual cytogenetic aberration or gene mutations may also be associated with prognosis (Bea et al., 1999; Cuneo et al., 1999; Salaverria et al., 2007; Nadeu et al., 2020). MYC protein and mRNA are usually expressed in a low number of cells in most cases of MCL and only highly expressed in a small subset of cases with blastoid morphology. MYC expression may be associated with MYC rearrangement, at least in a subset of cases (Hernandez et al., 1999; Hartmann et al., 2008; Oberley et al., 2013; Wang et al., 2020). High levels of MYC expression are associated with poor clinical outcome. TP53 expression is also more common in blastoid and pleomorphic variants, especially the later. TP53 expression, deletion and mutation are also a poor prognostic factor in MCL (Hernandez et al., 1996; Eskelund et al., 2017; Aukema et al., 2018; Nadeu et al., 2020). Recent genomic studies showed the prognostic significance of TP53 and *MYC* aberrations are independent of genomic complexity (Nadeu et al., 2020).

Summary

MCL is heterogeneous in all aspects. It has a spectrum of pathological and clinical characteristics and encompasses a large variety of architectural and cytological variants. Architecturally, it includes the isMCN, mzMCL, nodular MCL, and the most common diffuse pattern. Cytologically, it includes the classical one and 4 variants. *CCND1* translocation or t(11;14)(q13;q32) is the only common feature of MCL, presenting in >95% of MCL, except rare Cyclin D1 negative MCL. Most MCL cases have a typical immunophenotype, although a small subset demonstrates an atypical immunophenotype. The diagnosis relies on the integration of morphological and immunophenotypic features in typical cases, and genetic and molecular studies are required in a subset of cases with atypical features. The differential diagnosis is broad and associated with particular clinical and biological features. Although MCL has been considered as an aggressive B cell lymphoma, two distinct subtypes have been recognized, the more aggressive conventional type which represents the majority of MCL, and the indolent lnnMCL. Molecular cytogenetic evolution in MCL is rapid and helpful for the diagnosis, differential diagnosis, prognostic stratification, prediction of disease evolution, and development of new personalized therapeutic strategies. All these will in turn result in improved patient outcome.

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