*Article*

# Unusual variants of mantle cell lymphoma

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**Abstract:** Mantle cell lymphoma (MCL) is recognized as an aggressive and incurable small B-cell lymphoma and represents a group of t(11;14)(q13;q32)/*CCND1*+ neoplasms with a wide variety of morphology. Thus, the identification of various MCL variants is important for guiding appropriate therapies and predicting outcomes. Histopathologic diagnosis of classical MCL is usually straightforward due to its typical morphology and nuclear overexpression of cyclin D1. However, approximately 10% of the MCL are represented by its own morphologic variants, mimicking other lymphomas, including the challenging cyclin D1-negative MCL. Furthermore, typical MCL immunophenotype and genetic abnormalities may not be found in every case. Therefore, MCL variants may be a diagnostic trap for hematopathologists. Taking into account that histopathological diagnosis remains the gold standard for MCL diagnosis, this paper summarizes the practical approaches to the diagnosis of the uncommon variants of MCL in accordance with the 2016 revised WHO classification of lymphoid neoplasms.

**Keywords:** Mantle cell lymphoma, lymphoma variants, cyclin D1, Sox11, *in situ* mantle cell neoplasia, double hit lymphoma

## Introduction

Mantle cell lymphoma (MCL) is recognized as an aggressive and incurable small B-cell lymphoma which represents approximately 5% of all non-Hodgkin lymphomas [1]. This lymphoma is a mature lymphoid neoplasm characterized by the presence of t(11;14)(q13;q32), resulting in the *CCND1* (*PRAD-1*) gene fusion and cyclin D1 overexpression. It occurs more frequently in men at a median age of 60 years. Most patients present with late-stage disease, generalized lymphadenopathy, and liver involvement; bone marrow involvement occurs in more than 60% of the cases [2]. Peripheral blood involvement is found in approximately 25% of the cases [3]. However, fewer than half have systemic symptoms. Extranodal sites are also frequently involved, particularly bone marrow, Waldeyer ring, as well as the gastrointestinal tract, where multiple lymphomatous polyposis occurs [4]. Skin involvement is also well documented as a secondary manifestation of the systemic disease and the cutaneous presentation often preceded the diagnosis of systemic disease [5, 6].

Histopathologic diagnosis of classical MCL is usually straightforward due to its typical morphology and nuclear overexpression of cyclin D1. Typical MCL often shows a mantle zone pattern, vaguely nodular pattern or diffuse pattern. The tumor is composed of a monotonous population of small to intermediate lymphoid cells with dark nuclei, clumped chromatin, irregular nuclear membrane, inconspic-

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uous nucleoli and scant cytoplasm. Pseudofollicles, centroblasts, and immunoblasts are typically absent. Perivascular eosinophilic hyaline sclerosis and scattered epithelioid histiocytes are also present. MCL usually expresses the typical B-cell markers, such as CD19, CD20, CD79a, and PAX5, and shows variable (from weak to strong) but diffuse nuclear expression of cyclin D1 in almost all the cases; CD5 is often positive although CD5-negative cases are not uncommon [7]; expression of CD43 is also quite common while CD23, CD10 and BCL6 are generally negative.

Although cyclin D1 expression is highly specific for MCL, it is also expressed at variable intensities in approximately 40% of plasma cell myelomas associated with *IGH-CCND1* rearrangement, *CCND1* amplification, or no structural alterations of the *CCND1* locus [8]. It can also be weakly expressed in hairy cell leukemia and not associated with *CCND1* rearrangement [9, 10]. The most important histopathological prognostic factor is currently the proliferation index as assessed by Ki-67 staining [11]. Overexpression of p53 with a cutoff of 20% strong nuclear staining has been associated with shorter survival [12]. The characteristic t(11;14)(q13;q32) that juxtaposes the *CCND1* gene to the *IGH* gene may be detected by FISH analysis in the vast majority of typical cyclin D1+ MCL cases [13]. In a subset of MCL, *CCND1* can also be juxtaposed to *IGK* in t(2;11)(p11.2;q13) and *IGL* in t(11;22)(q13;p11.2) [14–16]. The current World Health Organization (WHO) guidelines for the diagnosis of MCL rely on morphologic examination and immunophenotyping, with demonstration of cyclin D1 protein overexpression and/or the t(11;14)(q13;q32) for confirmation. Nevertheless, the European Association for Hematopathology / Society for Hematopathology (EAHP/SH) [13] recommends that FISH analysis for t(11;14)(q13;q32) (or *IGH-CCND1* rearrangement) is not a requirement for the diagnosis of cyclin D1+ MCL cases.

The "classical" morphology is detectable in about 90% of MCL cases, while the remaining approximately 10% are considered MCL variants, which include the small cell variant (chronic lymphocytic leukemia-like), the monocytoid-like variant, the MCL with plasmacytic differentiation, the pleomorphic variant, the blastoid variant, and the challenging cyclin D1-negative MCL. Thus, diagnostic pitfalls do exist in MCL due to its variations in morphology and immunophenotype [17]. This article aims to review: 1) the uncommon morphologic variants of MCL and the practical approach to their differential diagnosis; 2) the diagnostic dilemma of cyclin D1-negative MCL; and 3) the uncommon clinical variant of MCL in accordance with the 2016 revised WHO classification of lymphoid neoplasms.

## Mantle Cell Lymphoma Variants

### *Monocytoid-like MCL*

Morphologic similarities are occasionally observed in MALT lymphoma and MCL; distinguishing them is difficult at times [18]. In fact, existence of the so-called marginal zone-like MCL has drawn much attention. As a matter of fact, neoplastic MCL cells rarely have round hyperchromatic nuclei with small inconspicuous nucleoli and abundant pale cytoplasm, resembling marginal zone B cells (monocytoid B cells) [Figure 1]. Furthermore, many cases demonstrated an interfollicular growth pattern when it involves either nodal or extranodal site, and follicular colonization may also be present, which are also features of marginal zone lymphoma (MZL), both nodal and splenic. This rare monocytoid-like variant may represent a challenge especially for the CD5-negative lymphomas at the extranodal locations, such as gastrointestinal tract, where extranodal MZL occurs quite frequently [19, 20].

Monocytoid-like MCL variant often expresses CD20, cyclin D1 and SOX11, while CD5 may be negative in a subset of cases [20]. However, immunoglobulin superfamily receptor translocation-associated 1 (IRTA1), a novel protein frequently expressed by neoplastic MZL cells, is negative [21]. FISH analysis with break-apart probes usually detects *IGH-CCND1* rearrangement [19, 22]. Due to their monocytoid-like

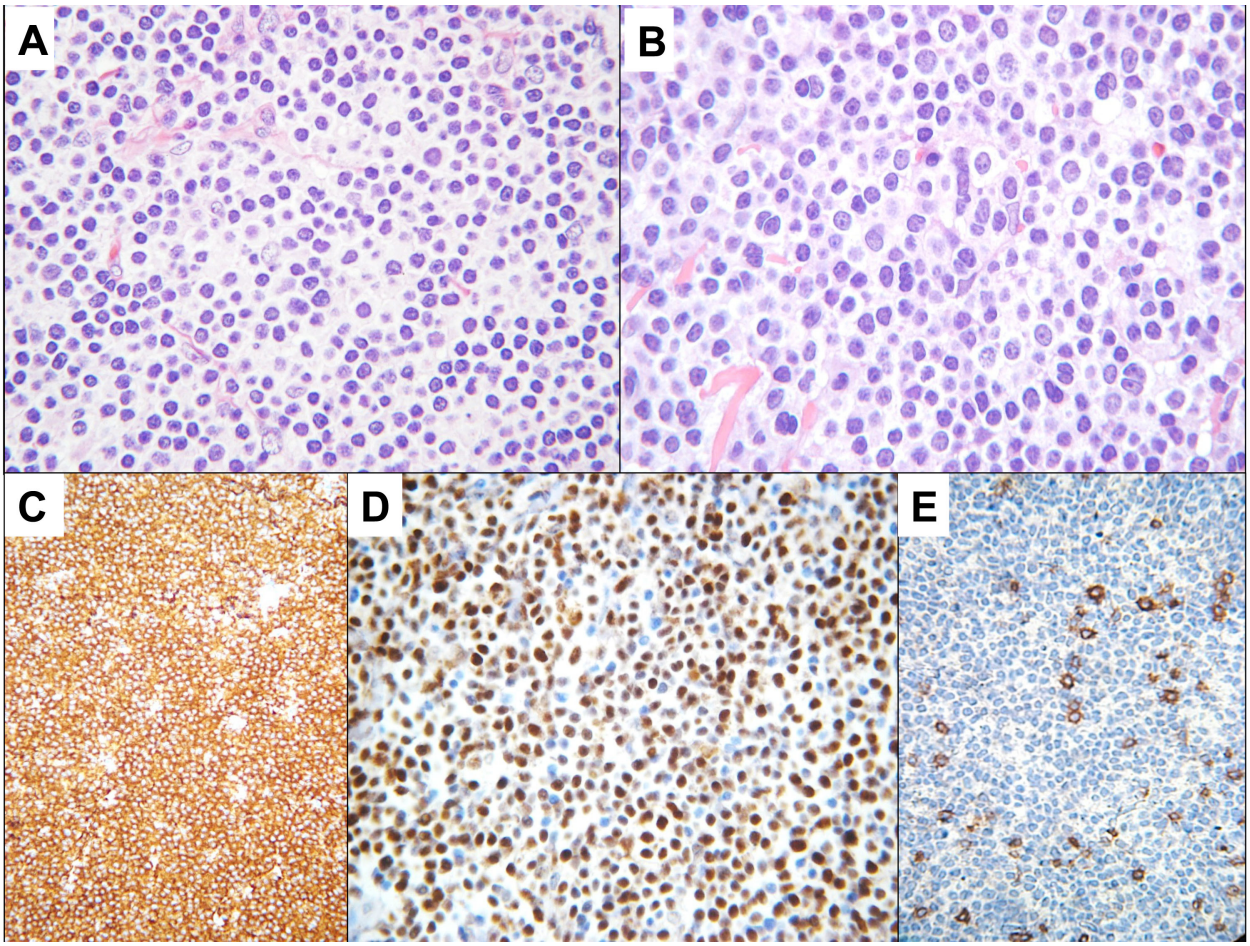


**Figure 1:** Monocytoid-like mantle cell lymphoma. The node is totally effaced by diffuse and vaguely nodular proliferation of small atypical lymphoid cells with round nuclei, regular nuclear membrane, clumped chromatin, small nucleoli, and a large amount of clear cytoplasm (A, H&E, original magnification x200; B, H&E, original magnification x400). The lymphoma cells show strong expression of CD20 (C, immunoperoxidase, original magnification x200), and cyclin D1 (D, immunoperoxidase, original magnification x200), but negativity for CD5 (E, immunoperoxidase, original magnification x200). All the stains in this paper were performed as previously described [100] with additional antibodies purchased from Dako, Denmark.

morphology and CD5 negativity, such MCL variants can be misdiagnosed as MZL and treated like MZL (less aggressively), resulting in an unfavorable outcome.

In contrast to MCL, MZL is an indolent B-cell lymphoma with heterogeneous cell morphology. The most characteristic morphology is the "monocytoid" B cells with abundant clear cytoplasm, a well-demarcated cell membrane, and round to slightly irregular nuclei. In addition, there may be smaller lymphocytes with irregular, indented nuclei and scarce cytoplasm, as well as variable proportion of larger blast-like cells with oval or round nuclei and prominent nucleoli.

In comparison with MCL, MZL cells are cyclin D1-negative and do not harbor t(11;14)(q13;q32). MZL is often negative for CD5, although CD5+ MZL have been reported [23]. Furthermore, the observed CD5 downregulation in MCL seems much more frequent than the reported 10% CD5 negativity in classical

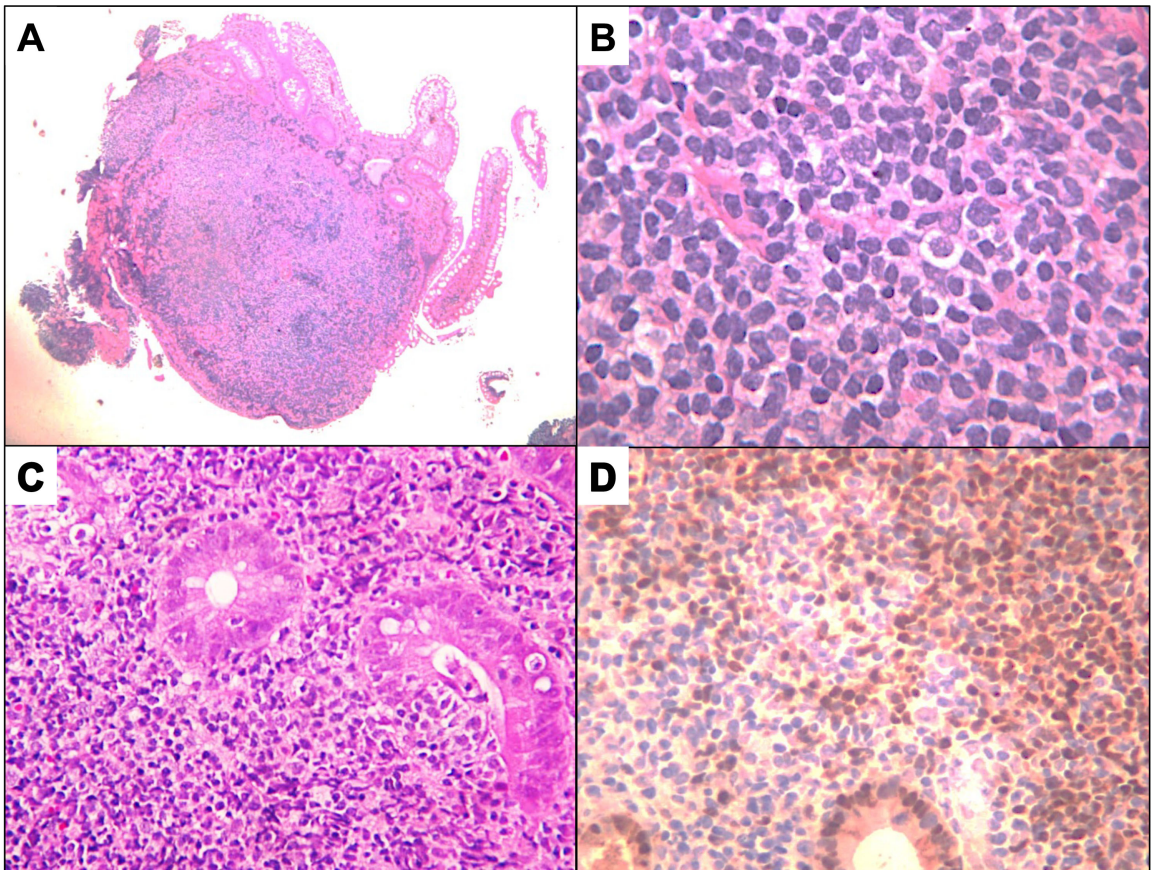


**Figure 2:** Extranodal mantle cell lymphoma involving gastrointestinal tract (lymphomatous polyposis). A portion of colonic mucosa/submucosa is totally effaced by nodular proliferation (A, H&E, original magnification x20) of small atypical lymphoid cells with round nuclei, irregular nuclear membrane, clumped chromatin, small or inconspicuous nucleoli and abundant clear cytoplasm B, H&E, original magnification x400). Prominent lymphoepithelial lesions are also present (C, H&E, original magnification x100). Lymphoma cells show diffuse expression of CD20, CD5, and cyclin D1 (D, immunoperoxidase, original magnification x200).

MCL. Combined with the unusual morphologic and immunophenotypic variations, such as monocytoid-like features and CD5 negativity, these MCL variants deceivingly mimic extranodal MZL if the cyclin D1 immunostain is not evaluated, likely leading to an incorrect diagnosis. These highlight the importance of comprehensive immunophenotyping including cyclin D1 in lymphomas with "monocytoid" morphology [24].

Involvement at extranodal sites such as gastrointestinal tract by MCL (the so called lymphomatous polyposis) is quite common. In this site, the neoplastic B cells of MCL show an invasive vaguely nodular pattern of growth with disruption of the glandular architecture [Figure 2]. Prominent lymphoepithelial lesions may also be present and if tumor B cells show a striking monocytoid-like feature, it mimics MALT lymphoma. CD5, CD23, cyclin D1 and SOX11 immunostains usually resolve the differential with MALT lymphoma.

### *MCL with plasmacytic differentiation*

Plasmacytic differentiation may occur in many small B-cell lymphomas, including MZL, lymphoplasmacytic lymphoma (LPL), chronic lymphocytic

leukemia/small lymphocytic lymphoma (CLL/SLL), and even follicular lymphoma (FL) [25]. However, plasmacytic differentiation is unusual in MCL. In fact, plasma cells are usually absent in MCL or, if present they have traditionally been regarded as part of the non-neoplastic background. The majority of MCL have been classically described as a monotonous population of mature B cells with no evidence of plasmacytic differentiation [26]. Nonetheless, occasional MCL with focal areas of plasmacytic differentiation have been reported [27]. Recent studies provide strong evidence that in this MCL variant plasma cells were usually clonal, in the majority of cases (70%) clearly demonstrating that the plasma cells and MCL cells can derive from the same B-cell clone [28].

This rare MCL variant shows mixed populations of small lymphoplasmacytic B cells and plasma cells. Amyloid deposition may also be present. The small lymphoid cells characteristically express CD20 and cyclin D1, and variably or do not express CD5; SOX11 is often negative, as well as CD23 and CD138. However, cytoplasmic immunoglobulin light chain restriction may be detected. Plasma cells do not express CD20 and PAX5, while CD138 and cyclin D1 are positive with cytoplasmic immunoglobulin light chain restriction. All the small neoplastic cells show lymphoplasmacytic and plasmacytic differentiation, including the ones with Dutcher bodies and strong nuclear expression of cyclin D1, supporting that they have the same neoplastic origin.

The mechanisms underlying plasmacytic differentiation of MCL are poorly understood. Recent observations suggest that terminal B-cell differentiation program (plasma cell differentiation) in MCL could be occurring mainly in SOX11-negative MCL, confirming the notion that absence of this transcription factor may allow MCL cells to progress towards plasma cell differentiation. Indeed, some studies show that SOX11 may influence MCL pathogenesis by blocking plasmacytic differentiation [29]. Furthermore, expression of the plasmacytic transcription factors, such as BLIMP1 and XBP1, is frequently seen in SOX11-negative rather than SOX11-positive lymphomas [30].

Differential diagnosis of MCL with plasmacytic differentiation certainly includes several small B-cell lymphomas with plasma cell differentiation. It is generally agreed that these tumors must be classified according to the atypical lymphoid component. Identification of cyclin D1 expression or the t(11;14)(q13;q32)/*IGH-CCND1* by FISH analysis may facilitate the diagnosis of MCL. However, given that plasmacytic differentiation in MCL is very rare and some of these MCL may be CD5-negative, recognition of a small B-cell lymphoma with plasmacytic differentiation as MCL may be challenging, especially for those CD5-negative small B-cell lymphomas associated with serum (IgM, IgG, or IgA) paraproteins.

Recent identification of MYD88 L256P mutations as a genetic hallmark of lymphplasmacytic lymphoma (LPL) may help in the differential diagnosis, and its absence would favor a different small B-cell lymphoma. However, MYD88 mutation is rarely found in SOX11-negative MCL with plasmacytic differentiation. Moreover, rare *IGH-CCND1* positive small B-cell lymphoma carrying the MYD88 mutation may suggest either a MCL with plasmacytic differentiation with late acquisition of MYD88 mutation or a LPL with a secondary acquisition of t(11;14)(q13;q32)/IGH-*CCND1* rearrangement and subsequent cyclin D1 overexpression. Taking into account that secondary acquisition of the t(11,14)(q13;q32) is also reported in rare CLL/SLL cases, this molecular finding indicates that, although rare, t(11;14)(q13;q32)/*CCND1*-IGH rearrangement could be a secondary event in small B-cell lymphomas [25].

Differential diagnosis with plasma cell myeloma with t(11;14)(q13;q32) should also be considered. However, MCL with plasmacytic differentiation is CD5 positive in 57% of the cases, and tends to present with generalized lymphadenopathy and leukemic involvement without lytic bone lesions; all these features are unusual in plasma cell myeloma. Finally, composite tumors consisting of MCL and

a clonally unrelated plasmacytoma or plasma cell myeloma have also been occasionally reported [31–33].

The distinction between MCL with a concomitant plasma cell neoplasm and a unique variant of MCL with plasmacytic differentiation has relevant clinical significance, since the prognosis and treatment of the two diseases would be different. Regarding this, demonstration of the *CCND1* translocation by itself is insufficient to discriminate between MCL with plasmacytic differentiation and MCL with concurrent plasma cell neoplasm, as the t(11;14)(q13;q32) is commonly found in non-hyperdiploid plasma cell myeloma. Therefore, plasmacytic differentiation in MCL represents a diagnostic pitfall. A multidisciplinary approach including detailed morphologic evaluation of the neoplastic populations and a large panel of immunostains, along with cytogenetic analysis for the t(11;14)(q13;q32), are needed to rule out other types of B-cell lymphomas with plasmacytic differentiation as well as plasma cell tumors.

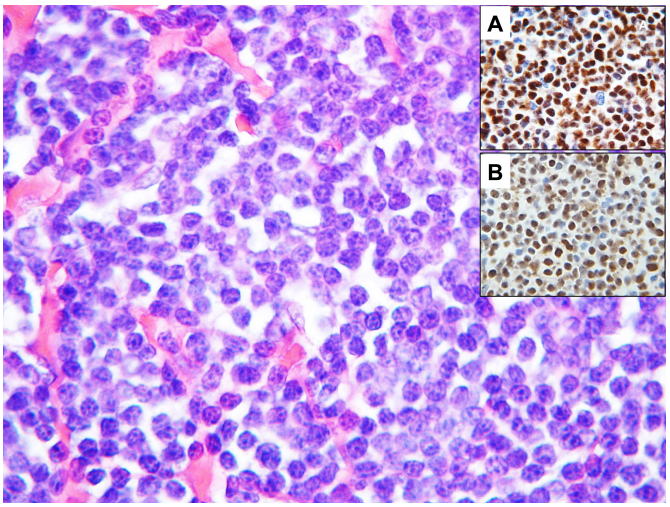


**Figure 3:** Mantle cell lymphoma, small-cell variant. This monomorphic lymphoid proliferation is composed of small cells with round and clumped nuclei, single or multiple inconspicuous nucleoli, and scant cytoplasm, likewise small prolymphocytes as in CLL/SLL (H&E, original magnification x 200). These cells show strong nuclear expression of Sox 11 (Inset A) and cyclin D1 (inset B) (immunoperoxidase, original magnification x100).

### *Prolymphocytoid MCL*

B-cell prolymphocytic leukemia (BCPL) is a rare disease, generally occurring in elderly people and making up <1% of all the mature B-cell malignancies. It is characterized by the presence of very high lymphocyte counts with >55% prolymphocytes, no or minimal lymphadenopathy and massive splenomegaly [34]. The neoplastic population is composed of small to medium-sized mature lymphocytes with coarse chromatin, slightly irregular nuclear contours and one or more prominent nucleoli. The immunophenotype ranges from cases similar to CLL/SLL to cases overlapping with MCL. Since a t(11;14)(q13;q32) involving the *IGH-CCND1* gene rearrangement is detectable in approximately 20% of the originally diagnosed BCPL, these BCPL cases are now considered to be MCL by the 2008 WHO Classification of Tumours of Hematopoietic and Lymphoid Tissues [35]. In fact, the prolymphocytoid variant of MCL/mantle cell leukemia has been well described [36–39]. Its similarity to classical MCL has also been confirmed by their similar gene expression profiles [40, 41].

### *MCL, small cell variant*

A small cell variant of MCL has recently been added to the WHO Classification. This small cell variant is composed of small lymphocytes with rounded nuclei, dense chromatin, and scant cytoplasm, mimicking chronic lymphocytic leukemia/small lymphocytic lymphoma (CLL/SLL) [Figure 3]. Although it is difficult to distinguish these two entities by cytology, prolymphocytes, paraimmunoblasts and proliferation centers are never found in this MCL variant. Nuclear expression and the intensity of cyclin D1 were weak and a considerable number of cases lacked SOX11 (58%). Bone marrow involvement, hepatosplenomegaly, leukemic changes, and non-nodal clinical features were more frequently identified in patients with small cell variant of MCL than in patients with classical MCL. Recent

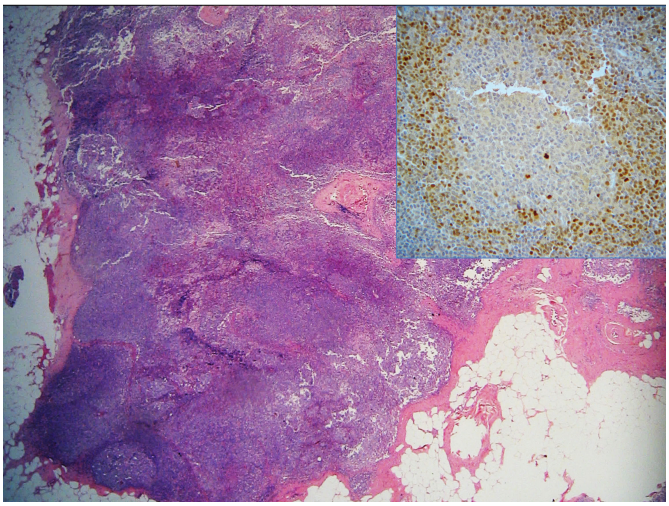

**Figure 4:** *In situ* mantle cell neoplasia. This small inguinal node was excised for unexplained lymphadenopathy. Low magnification reveals mantle zone hyperplasia (H&E, original magnification x20). A rim of mantle zone lymphocytes shows nuclear expression of cyclin D1 (Inset, immunoperoxidase with clone (SP4) antibody, original magnification x40).

data suggest that small cell variant of MCL constitutes a specific subset of indolent lymphoma with t(11;14)(q13;q32), characterized by bone marrow involvement, splenomegaly and a low Ki-67 proliferation index [42].

### *In situ MCL (In situ mantle cell neoplasia)*

Cases of nodal involvement by scattered cyclin D1+ neoplastic lymphocytes located in thin mantle zones surrounding reactive germinal centers are well described [43]. Identification of this "in situ MCL" is detectable only by immunohistochemical staining for cyclin D1, since lymph node architecture is well preserved [44, 45]. Probably the so-called "in situ MCL" represents the earliest immunophenotypically detectable MCL, in which the neoplastic cells identified by cyclin D1 staining are found exclusively confined to the inner mantle zone or narrow mantles of reactive germinal centers in otherwise morphologically unremarkable lymph nodes [Figure 4]. In situ mantle cell neoplasia is much less common than "in situ follicular lymphoma" and appears to have a low rate of progression. In fact, this lesion may represent a very early manifestation of MCL with a better prognosis and long-term survival even without therapy but, at least in some cases, it has also been found in association with full blown MCL and aggressive clinical progression [46].

In daily practice, in situ MCL is often an incidental finding because it is usually present with prominent germinal centers surrounded by apparently normal or minimally expanded mantle zones. In fact, morphologic findings in these cases suggest florid reactive follicular hyperplasia, while immunostaining for cyclin D1 reveals singly spread or partial mantle zone involvement by cyclin D1+ B lymphocytes. In situ MCL by itself does not cause significant lymphadenopathy and therefore it remains controversial whether it should be regarded as a malignancy.

### *Intrafollicular MCL*

In rare cases of "early" preclinical MCL neoplastic mantle cells may transit or localize to the germinal center, at least in a subset of cases, showing a very unusual "homing" to germinal centers with sparing of mantle zones and interfollicular areas. This particular early nodal involvement by MCL is characterized by neoplastic cells localized not within mantle zones but within reactive germinal centers where scattered cyclin D1+ B cells exhibit a "follicular in situ" growth pattern [47]. Generally, these scattered intrafollicular cyclin D1+ B cells are often identified retrospectively inside a lymph node removed for other clinical reasons such as solid tumor staging, before the diagnosis of a full blown MCL. Occasionally, no manifest or antecedent MCL is evident at the time of the lymph node biopsy. Nevertheless, some patients have clinically manifest disease but a relatively indolent course.

Routine morphologic examination of lymph node by H&E stain usually reveals reactive germinal centers of a morphologically hyperplastic lymph node although immunohistochemical stains show tightly

packed strongly cyclin D1+ small lymphocytes exclusively confined inside the otherwise reactive germinal centers with sparing of the mantle zones and interfollicular areas. In addition to cyclin D1, they express CD20 with co-expression of BCL2, CD5, and SOX11. Stains for CD10, BCL6, and CD23 are usually negative. The CD23+ follicular dendritic cell meshwork is preserved. At first sight this quite rare pattern of nodal infiltration by MCL may mimic follicular lymphoma in situ since both tumors express CD20 and BCL2 with a low Ki-67 proliferation rate. Nevertheless, coexpression of CD5 and cyclin D1 and negativity for CD10 and BCL6 in the tumor cells favor the diagnosis of MCL. When a lymph node is only minimally involved by a small number of MCL cells in a morphologically hyperplastic follicle, the intrafollicular MCL might be overlooked.

All these above mentioned cases underscore the difficulties in the daily practice of lymph node pathology, highlighting the need for complete immunophenotypic work-up together with ancillary studies such as FISH analysis for t(11;14)(q13;q32)/*IGH-CCND1* rearrangement to render a correct diagnosis [48]. Although extremely rare, intrafollicular MCL does exist and recognizing this particular MCL variant will avoid confusion with in situ follicular lymphoma and otherwise benign lymph node. Surgical pathologists and hematopathologists should be aware that this novel intrafollicular MCL may be overlooked without proper work-up for routine lymph node evaluation.

### *Cyclin D1-negative MCL*

The existence of cyclin D1 negative MCL has been controversial since the current World Health Organization guidelines for the diagnosis of MCL rely on morphologic examination and demonstration of cyclin D1 overexpression and/or the t(11;14)(q13;q32). Moreover, a particular subset of rare MCL lacking cyclin D1 expression and/or the t(11;14)(q13;q32)/*IGH-CCND1* rearrangement displays otherwise similar morphology and phenotype as the classical MCL has been reported [49, 50]. In fact, genomic profiling studies have shown that approximately 10% of MCL with an otherwise similar gene expression profile lacked the t(11;14)(q13;q32) and cyclin D1 expression, making diagnosis of MCL problematic in these cases [49, 50].

Because cyclin D1-negative MCL is rare and reliable criteria for its diagnosis are lacking, it is not well characterized. However, except for the blastoid and polymorphic variants, all the reported cyclin D1-negative MCL were morphologically similar to the classic MCL. Typically, these cases do not stain for cyclin D1 and lack the characteristic t(11;14)(q13;q32)/*IGH-CCND1* fusion gene. Nevertheless, these cases exhibit the typical pathologic findings of classical MCL and, more importantly, shared the gene expression signature of classical MCL by microarray analysis. Gene expression profiling is only available in a research setting but currently represents the most sensitive and specific method for identifying cyclin D1-negative MCL [49]. The genetics of t(11;14)(q13;q32)/cyclin D1-negative MCL is poorly understood.

Furthermore, recent studies detected novel cryptic translocations: t(2;14)(p24;q32)/*IGH-MYCN*, t(2;12)(p11;p13)/*IGK-CCND2* and t(6;14)(p21;q32)/*IGH-CCND3* rearrangements in MCL cases lacking t(11;14)(q13;q32) or variant *CCND1* rearrangement [51]. FISH screening using break-apart probes demonstrate that more than half (55%) of the cyclin D1-negative MCL cases carried CCND2 rearrangements with IG genes (*IGK-CCND2*, *IGL-CCND2*, and *IGH-CCND2*). These cyclin D1-negative MCL had high levels of cyclin D2 mRNA [52–54]. Reverse transcriptase polymerase chain reaction (RT-PCR) assay could detect cyclin D2 mRNA levels in these cyclin D1-negative MCL cases, although a validated cyclin D2 quantitative RT-PCR assay is not widely available in clinical laboratories [13]. Routine use of the immunohistochemical detection for cyclin D2 or cyclin D3 is not practical in recognizing cyclin D1-negative MCL because

these cyclins are frequently expressed in other small B-cell lymphomas as well. In this particular scenario, SOX11 has emerged as a useful marker in the diagnosis of MCL, being positive in 93-95% of cases. Since SOX11 is a highly specific marker for MCL and its expression is independent of cyclin D1 expression and *CCND1* translocation, it becomes a very useful marker for the identification of cyclin D1-negative MCL cases [55–57]. However, SOX11 is not unique to MCL as it can also be expressed in lymphoblastic lymphoma, Burkitt lymphoma, hairy cell leukemia, and T-cell prolymphocytic leukemia. Thus, SOX11 represents a very valuable and additional diagnostic tool for the diagnosis of MCL, particularly for recognizing cases of cyclin D1-negative MCL that were previously identified only by gene expression profiling.

Taking into account that cyclin D1-negative MCL may include morphologically aggressive MCL, such as blastoid and pleomorphic variants, utility of SOX11 becomes foremost important in diagnosing MCL. When a CD5+/cyclin D1-negative B-cell lymphoma with blastoid or pleomorphic morphology are encountered, stain for SOX11 will be useful in differentiating the cyclin D1-negative blastoid or pleomorphic variants of MCL from lymphoblastic B-cell lymphoma and CD5+ "de novo" diffuse large B-cell lymphoma (DLBCL) [58], albeit the sensitivity of SOX11 nuclear staining, however, may be lower for the blastoid and pleomorphic variants.

Generally, patients with cyclin D1-negative MCL have clinical features similar to those with classical MCL. Lymphadenopathy is the most common presentation and extranodal involvement is also quite common. Although there is no significant difference between the cyclin D1+ and cyclin D1-negative MCLs in clinical course and overall survival, correct identification of the cyclin D1-negative MCL is important for patient treatment and prognostication.

### *MCL with aberrant immunophenotypes*

Typical MCL expresses CD20, CD5, cyclin D1, and CD43, and are negative for CD10, CD23, BCL6 and IRF4/MUM1. However, immunophenotypically atypical variants are not uncommon in MCL [59]. MCL may be CD10 positive (8%), CD5 negative (12%), CD23 positive (21%), and rarely negative for cyclin D1 (see above) [60]. More studies also show that MCL are positive for SOX11 in 78% to 93% of cases, but negative for CD5 in about 10% of MCL [20, 61]. Then, CD5 negativity may represent a diagnostic pitfall and its absence doesn't exclude a diagnosis of MCL at nodal or extranodal sites. We may need to take into consideration that lack of CD5 expression may occur in virtually any MCL including monocytoid-like, blastoid or pleomorphic variants [62]. Furthermore, expression of germinal center associated antigens CD10 and BCL6 is also well documented in MCL [Figure 6], as well as 35% of MCL being positive for IRF4/MUM1 [63–65, 67].

Additionally, CD23 positivity is detected in approximately 25% of MCL [68–70]. Rare cases of MCL expressing CD8 have been also reported [71]. These findings suggest that including cyclin D1, CD5, and SOX11 stains in every small/medium-sized B-cell lymphoma expressing either IRF4/MUM1 and/or germinal-center associated markers may be necessary to identify MCL with aberrant immunophenotypes.

### *Blastoid variant of MCL*

Some cases of MCL consisting of medium-sized lymphoblastoid cells with round nuclei, finely dispersed chromatin, small indistinct nucleoli and a high mitotic rate (>20-30 mitoses/10 hpf), resembling lymphoblasts [Figure 5]. Although this variant often has a characteristic MCL immunophenotype, its phenotype can be heterogeneous; it can lack expression of CD5 as well as cyclin D1, but instead expresses CD10, BCL6, and CD23 [70, 72]. CD5- and cyclin D1-negative blastoid MCL might be underappreciated and easily classified into precursor B lymphoblastic

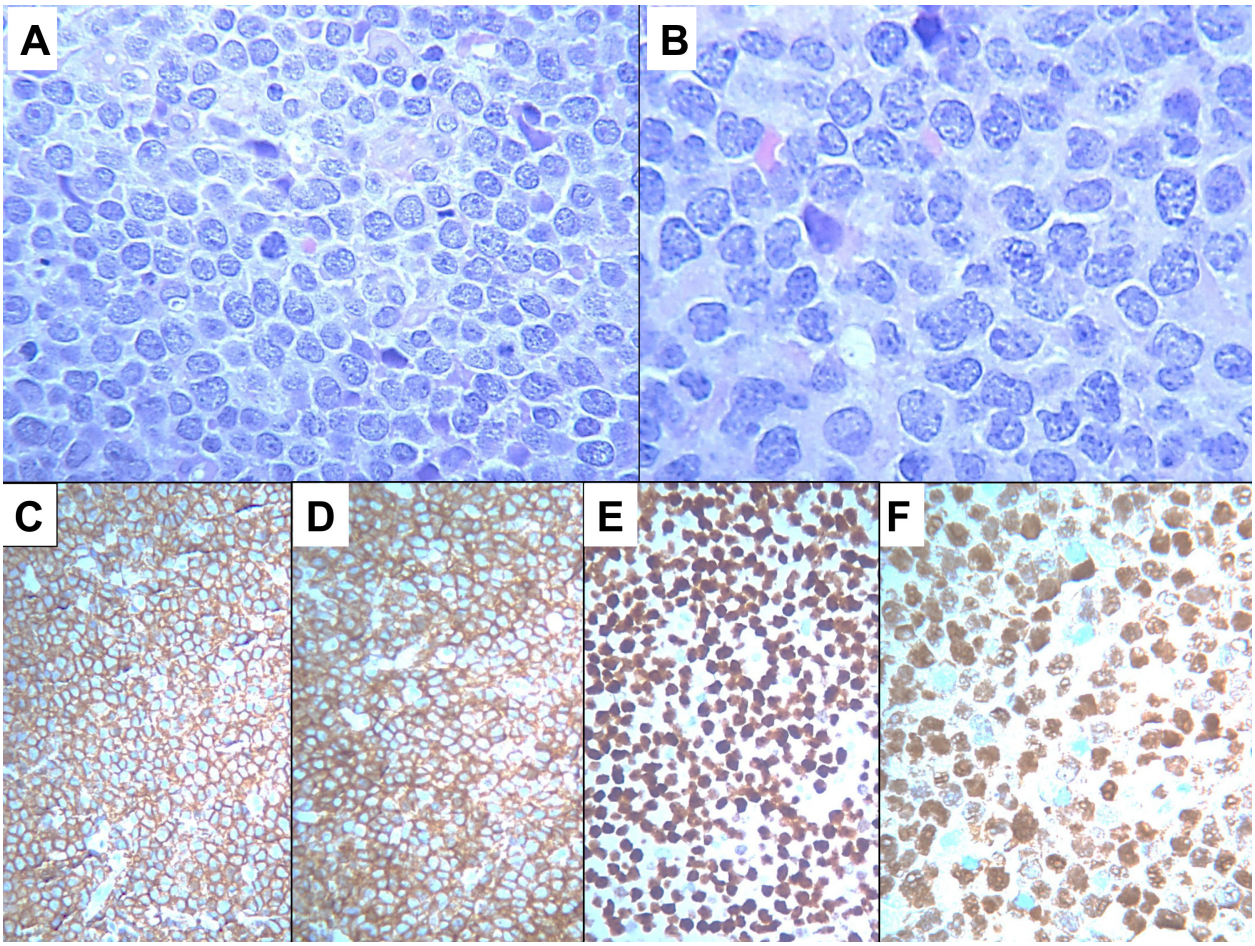


**Figure 5:** Mantle cell lymphoma, blastoid variant. (A) Proliferation of medium-sized atypical lymphoid cells with round nuclei, irregular nuclear membrane, finely dispersed chromatin, small inconspicuous nucleoli, and a rim of scant amphiphilic cytoplasm (A, H&E, original magnification, x200; B, H&E, original magnification x400). Stains show a diffuse expression for CD20 (C), CD5 (D), a high proliferation index by Ki67 (E) (immunoperoxidase, original magnification x100), and a nuclear expression of cyclin D1 (F) (immunoperoxidase, original magnification x200).

lymphoma [73], Burkitt Lymphoma and high-grade B-cell lymphoma, not otherwise specified, with rearrangement of *c-MYC*, *BCL2* and/or *BCL6* genes, the so called double-hit/triple-hit lymphomas. The blastoid variant of MCL occurs in 10-20% of all MCL patients and has a more aggressive clinical course and poor prognosis.

### *Pleomorphic variant of MCL*

The pleomorphic variant of MCL is composed of numerous pleomorphic intermediate-to-large cells with irregular nuclear contours, vesicular chromatin and prominent nucleoli [Figure 6]; the morphology mimics DLBCL. This variant represents an aggressive form of MCL and the cyclin D1 expression is the most reliable marker to distinguish it from the CD5+ "de novo" DLBCL [74]. Nonetheless, pleomorphic MCL may occasionally be negative for cyclin D1. When cyclin D1 is negative in the pleomorphic MCL, it might be diagnosed as CD5+ "de novo" DLBCL [73]. Cyclin D1 positivity in a large B-cell lymphoma often raises the possibility of a pleomor-

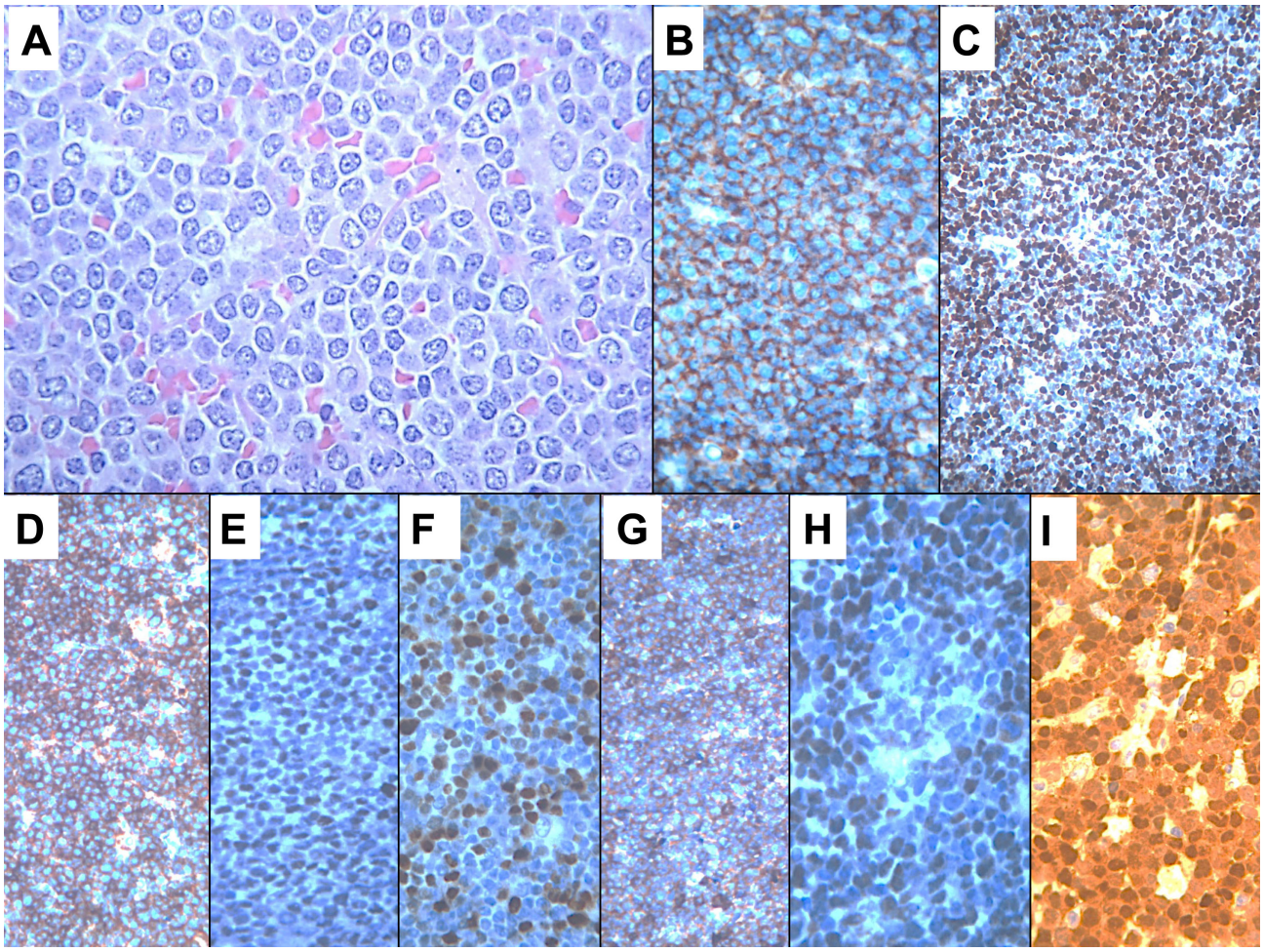


**Figure 6:** Mantle cell lymphoma, pleomorphic variant, with aberrant expression of germinal-center cell markers CD10 and BCL6, plus IRF4/MUM1. (A) This lesion shows a diffuse infiltration of large atypical lymphoid cells with round and vesicular nuclei, fine chromatin, single or multiple prominent nucleoli, and a rim of pale cytoplasm (H&E, original magnification x400). The lymphoma cells show diffuse expression of CD20 (B), Ki-67 (C), CD10 (D), BCL6 (E), IRF4/MUM1 (F), CD5 (G), Sox11 (H), and cyclin D1 (I) (immunoperoxidase, original magnification x200).

phic variant of MCL, which poses a challenge to distinguish it from the very rare (1.5-2%) cyclin D1+ DLBCL [Figure 7]. In fact, some of these DLBCL cases have nuclear expression of cyclin D1 but lack the t(11;14)(q13;q32) [75], or rarely express both CD5 and cyclin D1 [76], which makes it hard to distinguish it from MCL, particularly the pleomorphic variant [77]. FISH analysis for t(11;14)(q13;q32)/*IGH-CCND1* rearrangement may help to resolve this issue because of the usual absence of *CCND1* rearrangement in DLBCL.

However, *IGH-CCND1* rearrangement can rarely be seen in DLBCL, and the identification of *IGH-CCND1* with cyclin D1 overexpression in lymphomas with pleomorphic or blastoid morphology does not necessarily rule out a DLBCL [78]. In those troublesome cases, detection of BCL6 rearrangement by FISH analysis is supportive of the diagnosis of DLBCL despite the concurrent *CCND1* rearrangement. In fact, BCL6 rearrangement was not identified in any of the MCL, including the SOX11-negative MCL with aberrant BCL6+/ MUM1+ phenotype. Thus in

a cyclin D1+ high-grade lymphoma with pleomorphic morphology the BCL6+/MUM1+ immunophenotype favors but is not diagnostic of DLBCL. Although SOX11 is a marker highly specific for MCL, the absence of SOX11 per se cannot definitively distinguish DLBCL from the blastoid or pleomorphic variant of MCL (the absence of SOX11 is by no means diagnostic), although SOX11 expression in DLBCL is exceptional (only weak to moderate levels of expression) [79].

To avoid the diagnostic pitfall between pleomorphic variant of MCL and DLBCL, *IGH-CCND1* and cyclin D1 positivity need to be interpreted in the context of other clinical, immunophenotypic (in particular, SOX11 expression along with BCL6 and MUM1), cytogenetic, and molecular findings.

### *Double-hit MCL*

Deregulated expression of cyclin D1 is considered an initiating event in mantle cell lymphomagenesis, and high numbers of secondary chromosomal aberrations in MCL are related to tumor progression [80, 81]. Lymphomas with multiple recurrent chromosomal rearrangements, especially involving *MYC*, are referred to as "double-hit" (DH) lymphomas [82] and some studies reported that 10% of DH lymphomas carried *CCND1* and *MYC* rearrangements [83]. In non-Hodgkin lymphomas, a *MYC* rearrangement could be observed in up to 10% of DLBCL, with IG as the *MYC* partner in 60% of the cases. *MYC* deregulation in lymphoma may also occur as a secondary event in various lymphomas, including MCL. In fact, the abnormalities of the *MYC* gene locus are quite rare in MCL. MCL with both t(11;14)(q13;q32) and *MYC* rearrangement are often associated with an aggressive clinical behavior and blastoid morphology, and have been reported in only a limited number of cases [84–89].

MCL with a MYC+ immunopehotype has not been sufficiently evaluated. MCL with 8q24 abnormalities involving *MYC* gene is rare and often associated with blastoid morphology. Some authors have recently described the coexistence of t(11;14)(q13;q32) translocation and *MYC* rearrangement, manifesting as an *IGH-CCND1/MYC*, in blastoid variant of MCL [86]. Furthermore, as occurring in blastoid variant of MCL, lack of CD5 and/or cyclin D1 expression is not quite uncommon [62]. FISH, comparative genomic hybridization (CGH) or single nucleotide polymorphism (SNP) microarray should be recommended in evaluating blastoid MCL although these assays are not yet widely utilized in routine practice. *MYC* activation in B-cell lymphomas indicates a universally aggressive clinical course. In fact, high MYC IHC scores in MCL is associated with; 1) high-grade histology; 2) high proliferation index (by Ki-67 staining); and 3) high TP53 expression. Overexpression of MYC, Ki-67 and TP53 were independent predictors of shortened overall survival and progression-free survival in patients with MCL. Thus, overexpression of either MYC or TP53 should be included among the major MCL prognostic factors, and the MCL with a MYC IHC score >20% should be examined for *MYC* amplification or translocation by FISH analysis [90].

In contrast to Burkitt lymphoma, secondary *MYC* translocation in other B-cell lymphomas including MCL usually occurs in an unstable genome with complex karyotype and juxtaposed to non-IG gene locus. MCL with both *CCND1* and *MYC* gene rearrangements are specified as DH MCL even though the "second hit" by deregulated *MYC* is not usually mediated by chromosomal translocation. Although MCL with *MYC* amplification cannot be categorized as DH lymphomas in a literal sense, the clinicopathological significance might be identical to that of DH lymphomas. In fact, accumulation of other genetic events following the cyclin D1 rearrangement not only reflects dramatic genetic instability but also represents a marker of aggressive clinical course [84].

The so called "double hit MCL with *MYC* abnormalities" probably represents a relatively new and unique group of MCL with highly aggressive clinical behavior and poor clinical outcome. As a matter of fact, a recent study shows that 1.5% of

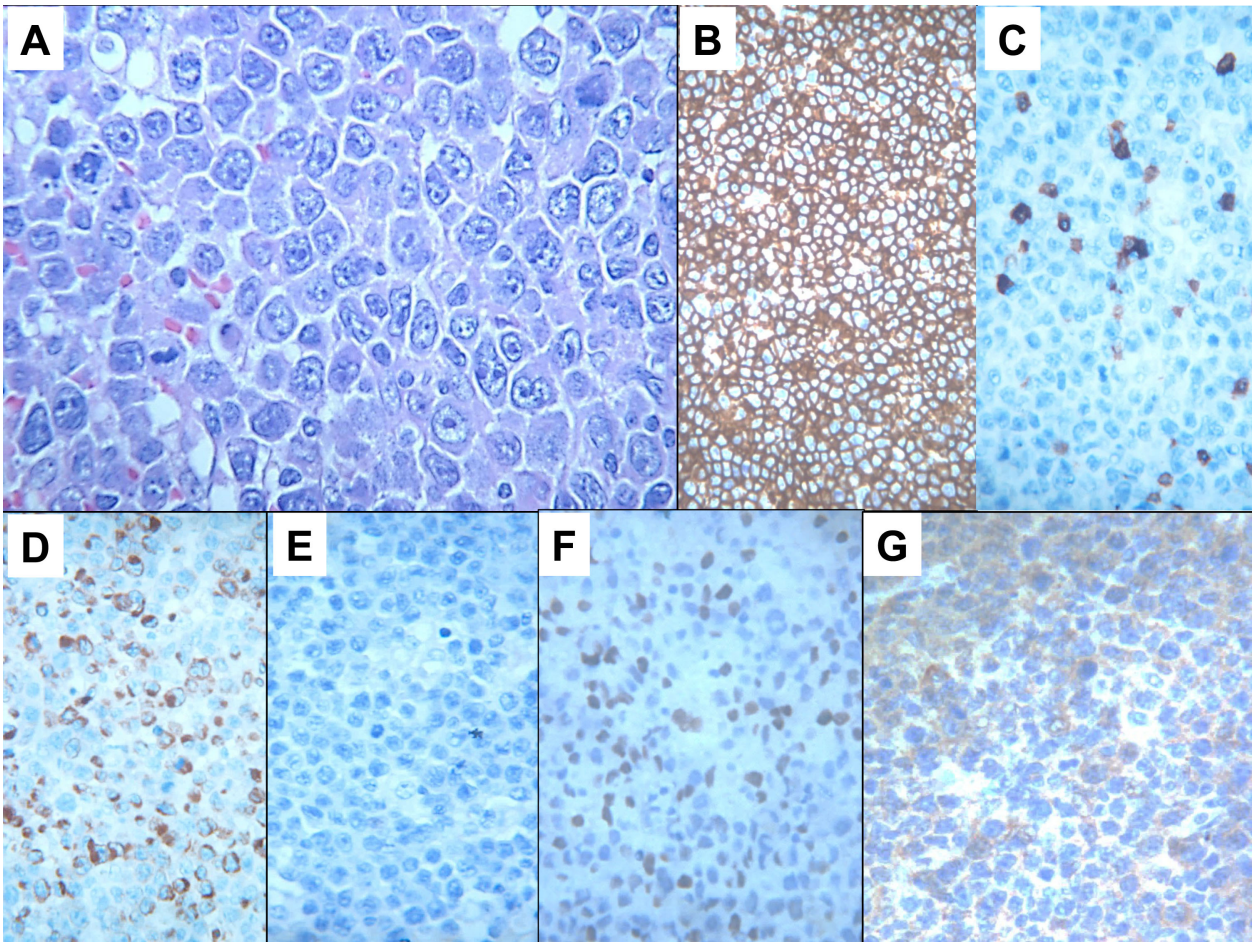


**Figure 7:** Cyclin D1+ DLBCL, NOS. (A) Proliferation of large lymphoid cells with round and vesicular nuclei, fine chromatin, single or multiple prominent nucleoli, and basophilic cytoplasm (H&E, original magnification x400). These cells show diffuse expression of CD20 (B) (immunoperoxidase, original magnification x100), focal expression of cyclin D1 (F), and cytoplasmatic lambda light chain restriction (D & E) (immunoperoxidase, original magnification x200). They are negative for CD5 (C) and SOX11 (G) (immunoperoxidase, original magnification x200).

MCL have *MYC* rearrangement, exclusively confined to MCL with blastoid or pleomorphic morphology. This study suggests that these cases of MCL with *MYC* rearrangement be designated DH MCL [91]. Identification of such DH MCL warrants aggressive Burkitt-type chemotherapy, as complete remission can be achieved, although presence of *MYC* translocation in this setting is typically associated with a short disease free survival and an aggressive clinical course [92].

*MCL with prominent intrasinusoidal pattern in bone marrow*

Occasionally, bone marrow is the primary site of malignant lymphomas [Figure 8]. Bone marrow involvement by MCL is frequent, being reported in more than 2/3 of cases. This involvement may range from minimal and focal to diffuse replacement of hematopoietic tissue. Intrasinusoidal infiltration by lymphoma cells is a typical finding in splenic marginal zone lymphomas (SMZL) involving the BM [93], although this predominant pattern of in-

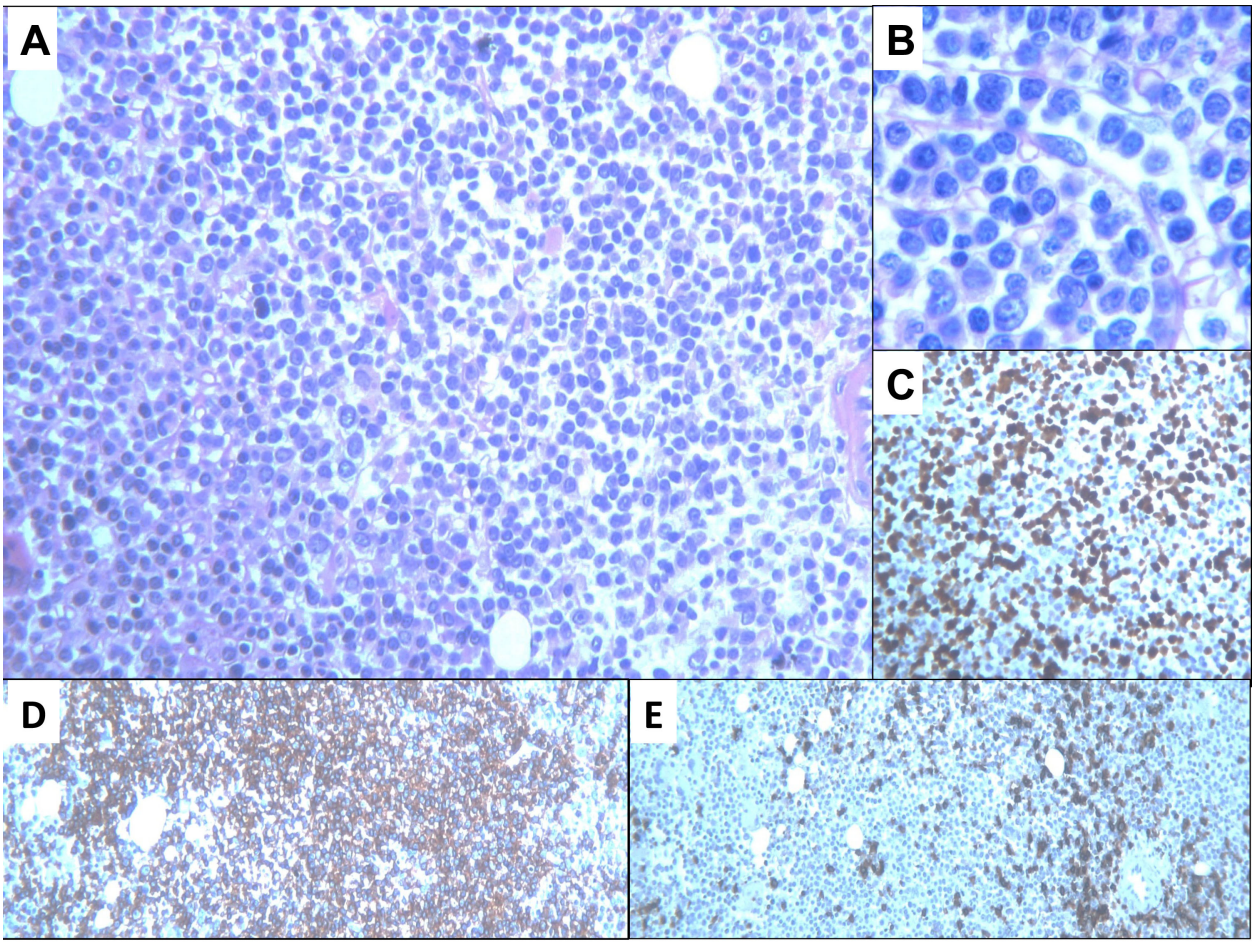


**Figure 8:** CD5-negative mantle cell lymphoma - intrasinusoidal involvement of bone marrow. Medium (A) and high power magnification (B) shows a portion of bone marrow with interstitial and intrasinusoidal infiltration of small atypical lymphoid cells with irregular nuclear contour, clumped chromatin, and inconspicuous nucleoli (H&E, original magnification x100 & x400, respectively). These cells show expression of CD20 (D, immunoperoxidase, original magnification x40) and cyclin D1 (C, immunoperoxidase, original magnification x40). They are negative for CD5 (E, immunoperoxidase, original magnification x40).

filtration is not specific for SMZL, being shared by large granular lymphocyte leukemia, hepatosplenic T-cell lymphoma, anaplastic large cell lymphoma, and intravascular large B-cell lymphoma [94]. MCL rarely also presents with a predominantly sinusoidal pattern of marrow involvement. Thus, in the setting of a predominantly small B-cell intrasinusoidal infiltration of the marrow, it is mandatory to stain for CD5 and cyclin D1 to exclude MCL [95].

*Indolent MCL*

The clinical course of MCL is typically aggressive. However, the existence of a subset of MCL with an indolent clinical course and long survival >5 years has been established beyond any doubt. Recently, two groups of clinically indolent MCL -SOX11 negative, non-nodal and leukemic MCL- are now recognized, supporting the speculation that MCL develops along two different pathways [96]. *In situ* mantle cell neoplasia also shows a low rate of pro-

gression requiring a conservative approach. In fact, MCL with indolent clinical course that does not require treatment at diagnosis has been identified, suggesting that the biology of these lymphomas may be more heterogeneous than initially thought. These MCL are composed of SOX11-negative IGHV-mutated B-cells which usually show a stable genome without many secondary genetic aberrations other than t(11;14)(q13;q32) and a characteristic gene expression profile. Clinically, these tumors present predominantly with non-nodal, leukemic disease involving peripheral blood and bone marrow and splenomegaly, thus also called as "leukemic non-nodal MCL". These cases are often clinically indolent [97–100].

## Conclusion

MCL consists of a group of *CCND1*+ neoplasms with a wide variety of morphology. These facts suggest that the identification of various MCL variants is important for guiding appropriate therapies or predicting clinical outcomes. The reported MCL variants exemplify the challenge we experienced in diagnosing MCL, because histopathological features of rare MCL can be substantially different from those described for the classical ones. Furthermore, typical MCL immunophenotype may not be found in every case. The histopathological features remain the gold standard for MCL diagnosis, which includes morphological variations, growth patterns, cytological subtypes, proliferative indices, immunophenotypes, and genetic abnormalities.

## Acknowledgements

The author claims no conflict of interest. The author thanks Prof. X. Frank Zhao for his precious advices, support and revision of the manuscript.

**Received**: February 10, 2017 **Accepted**: April 16, 2017 **Published**: May 11, 2017

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