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# Mantle Cell Lymphoma (MCL) Pathology and Diagnosis

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## Abstract

Mantle Cell Lymphoma (MCL) is a rare sub-type of B-cell Non-Hodgkin Lymphoma (NHL), with variable course. Most of patients with this disease has an aggressive clinical course and poor prognosis that remains incurable for the majority of patients. MCL has been categorized according to WHO 2016 update of lymphoid malignancies into two major subgroups Nodal and Leukemic non-nodal MCL, which are distinct in clinical presentation and molecular features. Therefore, accurate histological biopsy diagnosis is paramount in this rare sub-type of NHL. The differential diagnosis for MCL includes other non-Hodgkin lymphomas composed of small to medium-sized cells, most notably Chronic Lymphocytic Leukaemia (CLL)/Small Lymphocytic Lymphoma (SLL), Follicular Lymphoma (FL), Marginal Zone Lymphoma (MZL), and lymphoblastic lymphoma. An accurate diagnosis of MCL is of great importance, since this tumour generally carries a poor prognosis and requires more aggressive and novel treatment regimens. While, the leukemic indolent variant should be considered for observation. The diagnosis of high-grade variants of MCL is a particular challenge, as these tumours exhibit a broad spectrum of morphologic findings that can be misinterpreted as other types of NHL. The molecular basis of MCL highlights the biologic role as diagnosticand prognostic aids and as targetable by novel therapies.

***Keywords:*** Mantle cell lymphoma; Diagnosis; Pathology; Non-hodgkin lymphoma

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## Introduction

Mantle Cell Lymphoma (MCL) is a rare sub-type of B-cell Non-Hodgkin Lymphoma (NHL), with variable course. Most of patients with this disease has an aggressive clinical course and poor prognosis that remains incurable for the majority of patients. However, a minority of patient may survive untreated for many years [1-2]. The median age at diagnosis is 65 years and most patients with MCL have advanced stage disease at diagnosis (70%). While approximately 75% of patients initially present with lymphadenopathy, extra-nodal disease is the primary presentation in the remaining 25% [3].Common sites of involvement include the lymph nodes, spleen (45-60%), Waldeyer's ring, bone marrow (>60%), blood (13-77%), and extra-nodal sites, such as the gastrointestinal tract, breast, pleura, and orbit [4,5]. MCL is responsive to a variety of initial therapies, but relatively short-term remissions are achieved with conventional chemotherapy regimens. The Mantle cell lymphoma International Prognostic Index (MIPI) is the most commonly used prognostic scoring system to predict which patients will have a more aggressive clinical course [6]. MCL has been categorized according to WHO 2016 update of lymphoid malignancies into two major subgroups Nodal and Leukemic non-nodal MCL, which are distinct in clinical presentation and molecular features [7]. Therefore, accurate histological biopsy diagnosis is paramount in this rare sub-type of NHL.

## Pathology of MCL

### Pathogenesis

The pathogenic hallmark in MCL is the *t*(11;14)(q13;q32) translocation, with resultant over-expression of cyclin D1 causing cell cycle disruption [8]. The Classical (Nodal) MCL is believed to arise from naïve pre-germinal center B cells of the mantle zone that express SOX11, and typically involves lymph nodes and extra-nodal sites such as the gastrointestinal tract. More aggressive forms of MCL with blastoid or pleomorphic morphologies could represent disease progression. The other type of MCL (Leukemic / non-nodal) develops from antigen-experienced SOX11-negative B-cells from marginal zone or peripheral blood memory B cells. It mainly involves the peripheral blood, bone marrow, and spleen and is often clinically indolent, not requiring treatment.

### Morphology

The histologic growth pattern of MCL in lymph nodes is variable and it may be diffuse, nodular, or mantle zone, or a combination of these patterns. The most common pattern is an infiltrate mainly composed of small to medium-sized lymphoid cells, with slightly irregular or "notched" nuclei and inconspicuous nucleoli. However, the morphology can range from small, more irregular lymphocytes to lymphoblast-like cells (in the blastoid variant) and even occasionally to mixtures of small and large cells or markedly atypical large cells (in the pleomorphic variant) [9,10]. When malignant effusions are present, the cytological features of the tumour cells from the effusion are similar to those seen with peripheral blood involvement.

### Immunophenotype

MCL cells express high levels of surface IgM and IgD and with, lambda light chain restriction in the majority (80%) of cases. They also express pan-B cell antigens (eg, CD19, CD20), CD5, and FMC7 and dim/negative CD23, dim/negative CD200 and strong cyclin D1 expression) is frequent. Rare cases may be CD5– or CD23+ has been reported.

**Cyclin D1** - In the majority of MCL (95%) cases the immuno-histochemical analysis of involved nodal /extra-nodal tissues show a strong nuclear staining for cyclin D1 (BCL1) expression, which is not expressed in normal B- lymphocytes, including those that are CD5 negative [11]. Over-expression of cyclin D1 in MCL is strongly associated with the *t*(11;14)(q13;q32), translocation between the *CCND1* locus and the Immunoglobulin Heavy chain (*IgH*) locus [12,13]. The *t*(11;14) translocation, which is not specific for MCL as it occurs in a subset of multiple myelomas and rarely in other lymphoid malignancies [14]. It is seen in a little over half of patients on conventional cytogenetics, but on a much higher percentage of patients screened with Fluorescence InSitu Hybridization (FISH). This translocation leads to the dysregulated expression of *CCND1*, the gene that encodes cyclin D1, which is involved in the control of the G1 phase of the cell cycle. Cyclin D1 over expression is useful in distinguishing MCL from other relatively indolent B cell lymphomas, such as CLL / SLL, follicular lymphoma, lymphoplasmacytic lymphoma, and splenic marginal zone lymphoma [15]. Cyclin D1 may be overproduced even in cases lacking the *t*(11;14), suggesting that other types of acquired genetic aberrations. The gene expression profiles of cyclin D1 positive and negative "MCL" were very similar, and that tumours that failed to express cyclin D1 instead over-expressed either cyclin D2 or D3, which are highly homologous and functionally identical to cyclin D1. In this well characterized group of cyclin D1 negative and positive tumours, no difference in clinical behaviour or outcome was observed.

**SOX11 -** Is a neural transcription factor involved in central nervous system, which is not normally expressed in B cells and rarely expressed in other lymphoid neoplasm [7]. It is over-expressed in nodal MCL sub-type, while the leukemic non-nodal sub-type is associated with SOX11 negativity. SOX11 has been reported to block B cell differentiation, suggesting that it has a direct role in MCL pathogenesis [16]. SOX11 expression is also a useful marker MCL, particularly in rare cases that do not express cyclin D1 development.

SOX11 expression in MCL have produced conflicting results, overexpression of SOX11 appears to confer a worse prognosis [17,18]. In addition, cases of cyclin D1 negative, cyclin D2 negative, SOX11-positive MCL with an aggressive clinical course have been described [18].

## Genetic features

MCL is associated with the highest degree of genomic instability of the B cell malignancies, and a large number of secondary chromosomal alterations have been described [19]. *TP53* mutation, in particular, which is 15-20% more common in the blastoid variant, confers a dismal prognosis in MCL with a median

survival of 1.3 years versus 5.1 years for non-mutated disease (p=0.023) [20]. In contrast, the prognostic relevance of 17p deletion in MCL is less clear, although several studies have indicated an association with shortened survival [21]. Immuno-Globulin (Ig) heavy and light chain genes are rearranged. The Ig V region genes lack somatic mutations in most cases [22], indicating a pre-germinal center stage of differentiation, consistent with an origin from immunologically naïve mantle zone B cells.

Karyotyping of metaphase chromosomes reveals the *t*(11;14) in only 50-65% of MCLs, but by Fluorescence In Situ Hybridization (FISH) a much higher fraction of cases with cyclin D1 over-expression contain *CCND1/IgH* fusion genes [23]. Other genes associated with the cell cycle may also be expressed abnormally, including rearrangement of *CCND2* (cyclin D2) in cyclin D1 negative cases, mutations of the CDK inhibitors, p16 and p17 (particularly in blastoid variants), decreased expression of the CDK inhibitor p27, and disturbances of pathways associated with apoptosis [18,24]. Acquisition of a translocation involving the oncogene *MYC* has been associated with shorter survival [25]. Alterations in TP53, p16, p18, p21, and p27 may also play a role in the development and evolution of MCL [26]. Use of gene expression profiling, comparative genomic hybridization, proteomics, and deep sequencing of MCL genomes may shed additional light on the biology and clinical heterogeneity of MCL [27,28].

Other studies have identified activating NOTCH1 mutations in a minority of MCL cases, a finding that may predict a worse clinical outcome [28], additional work is needed to confirm this association. Deletion of or point mutations in the Ataxia Telangiectasia Mutated (*ATM*) tumour suppressor gene (11q22-q23) are seen in approximately one-third to one-half of MCL cases. Microarray studies have suggested that MCL cases display disturbances of pathways associated with apoptosis [29]. Specifically, MCL cells appear to avoid programmed cell death (apoptosis) by the expression of B cell lymphoma 2 (BCL2), upregulation of the PI-3 kinase/AKT pro-survival signalling pathway, activation of nuclear factor-kB (NF-kB), and mutations in *TP53*. Inhibitor for these pro-survival signalling pathways has revolutionised MCL treatment.

## Differential diagnosis

The differential diagnosis for MCL includes other non-Hodgkin lymphomas composed of small to medium-sized cells, most notably Chronic Lymphocytic Leukaemia (CLL)/Small Lymphocytic Lymphoma (SLL), Follicular Lymphoma (FL), Marginal Zone Lymphoma (MZL), and lymphoblastic lymphoma. Both MCL and CLL are neoplasms of small to medium-sized lymphoid cells with similar immunohistochemistry. While CLL is positive for CD20, CD5, and CD23, MCL is positive for CD20 and CD5 but negative for CD23. Immunohistochemistry for cyclin D1 is very helpful in excluding CLL. Other discriminating markers include SOX11 (typically positive in MCL) and LEF1 (frequently positive in CLL). Occasionally screening for *t*(11;14) by FISH is required to confirm MCL diagnosis [30].

MCL with predominant nodular growth pattern on histology may resembles that of follicular lymphoma. However, in contrast to follicular lymphoma, MCL cells are usually CD10–, CD5+, CD43+, and cyclin D1+. Like MCL, follicular lymphoma can present with gastrointestinal involvement as lymphomatous polyposis; such tumours are also best distinguished from MCL by immunohistochemistry. Both extra-nodal Marginal Zone Lymphoma (MZL) and MCL can involve the gastrointestinal tract and are neoplasms of small to medium-sized B lymphocytes. On immunophenotype, MCL expresses CD5 and cyclin D1 while extra-nodal MZL does not.

In addition, MZL often contains monocytoid B cells and shows plasmacytic differentiation, which are not features of MCL. The blastoid variant of MCL has a high mitotic rate and is often comprised of intermediate-sized cells with dispersed chromatin, irregular nuclear contours, and scant cytoplasm that mimic the appearance of lymphoblastic lymphoma. These cases are easily distinguished from lymphoblastic lymphoma by immunohistochemistry, as blastoid variant MCL expresses cyclin D1 and mature B cell markers (eg, surface immunoglobulin), whereas B lymphoblastic lymphomas lack surface immunoglobulin and express TdT, and T lymphoblastic lymphomas express TdT and additional T cell markers besides CD5.

## Conclusion

Mantle Cell Lymphoma (MCL) is a clinicopathologic entity with distinctive morphologic and immunophenotypic features and a characteristic cytogenetic abnormality, the *t*(11;14)(q13;q32). An accurate diagnosis of MCL is of great importance, since this tumour generally carries a poor prognosis and requires more aggressive and novel treatment regimens. While, the leukemic indolent variant should be considered for observation. The diagnosis of high-grade variants of MCL is a particular challenge, as these tumours exhibit a broad spectrum of morphologic findings that can be misinterpreted as other types of NHL. The molecular basis of MCL highlight the biologic role asdiagnostic and prognostic aids and as targetable by novel therapies.

## References


1. Harel S, Delarue R, Ribrag V, Dreyling M and Hermine O. Treatment of Younger Patients With Mantle Cell Lymphoma. Seminars in Hematology. 2011; 48(3): 194-207.
2. Vose JM. Mantle cell lymphoma: 2013 update on diagnosis, risk-stratification, and clinical management. American Journal of Hematology. 2013; 88(12): 1082-8.
3. Argatoff LH, Connors JM, Klasa RJ, Horsman DE and Gascoyne RD. Mantle cell lymphoma: A clinicopathologic study of 80 cases. Blood. 1997; 89(6): 2067-78.
4. Romaguera JE, Medeiros LJ, Hagemeister FB, Fayad LE, Rodriguez MA, Pro B, et al. Frequency of gastrointestinal involvement and its clinical significance in mantle cell lymphoma. Cancer. 2003; 97(3): 586-91.
5. Ferrer A, Salaverria I, Bosch F, Villamor N, Rozman M, Beà S, et al. Leukemic involvement is a common feature in mantle cell lymphoma. Cancer. 2007; 109(12): 2473-80.
6. Hoster E, Dreyling M, Klapper W, Gisselbrecht C, Van Hoof A, et al. A new prognostic index (MIPI) for patients with advanced-stage mantle cell lymphoma. Blood. 2008; 111(2): 558-65.

7. Swerdlow SH, Campo E, Pileri SA, Harris NL, Stein H, Siebert R, et al. The 2016 revision of the World Health Organization classification of lymphoid neoplasms. Blood. 2016; 127(20): 2375-90.

8. Swerdlow SH, Campo E, Harris NL, Jaffe ES, Pileri SA, Stein H, et al. WHO Classification of Tumours of Haematopoietic and Lymphoid Tissues. World Health Organization Calssification of Tumours of Haematopoietic and Lymphoid Tissue (Vol. 4th). 2008.

9. Zukerberg LR, Medeiros LJL, Ferry JA and Harris NL. Diffuse low-grade B-cell lymphomas: Four clinically distinct subtypes defined by a combination of morphologic and immunophenotypic features. Am J Clin Pathol. 1993; 100(4): 373-85.

10. Banks PM, Chan J, Cleary ML, Delsol G, De Wolf-Peeters C, Gatter K, et al. Mantle cell lymphoma: A proposal for unification of morphologic, immunologic, and molecular data. Am J Surg Pathol. 1992; 16(7): 637-40.

11. Liu Z, Dong HY, Gorczyca W, Tsang P, Cohen P, Stephenson CF, et al. CD5- mantle cell lymphoma. American Journal of Clinical Pathology. 2002; 118(2): 216-24.

12. Bertoni F, Zucca E and Cotter FE. Molecular basis of mantle cell lymphoma. British Journal of Haematology. 2004; 124(2): 130-40.

13. Martin P, Chadburn A, Christos P, Weil K, Furman RR, Ruan J, et al. Outcome of deferred initial therapy in mantle-cell lymphoma. J Clin Oncol.2009; 27(8): 1209-13.

14. Panayiotidis P and Kotsi P. Genetics of small lymphocyte disorders. Seminars in Hematology. 1999; 36(2): 171-7.

15. Yatabe Y, Suzuki R, Tobinai K, Matsuno Y, Ichinohasama R, Okamoto M, et al. Significance of cyclin D1 overexpression for the diagnosis of mantle cell lymphoma: A clinicopathologic comparison of cyclin D1-positive MCL and cyclin D1-negative MCL-like B-cell lymphoma. Blood. 2000; 95(7): 2253-61.

16. Vegliante MC, Palomero J, Pérez-Galán P, Roué G, Castellano G, Navarro A, et al. SOX11 regulates PAX5 expression and blocks terminal B-cell differentiation in aggressive mantle cell lymphoma. Blood. 2013; 121(12): 2175-85.

17. Nygren L, Wennerholm SB, Klimkowska M, Christensson B, Kimby E and Sander B. Prognostic role of SOX11 in a population-based cohort of mantle cell lymphoma. Blood. 2012; 119(18): 4215-23.

18. Salaverria I, Royo C, Carvajal-Cuenca A, Clot G, Navarro A, Valera A, et al. CCND2 rearrangements are the most frequent genetic events in cyclin D1 - mantle cell lymphoma. Blood. 2013; 121(8): 1394-402.

19. Jares P, Colomer D and Campo E. Genetic and molecular pathogenesis of mantle cell lymphoma: perspectives for new targeted therapeutics. Nat. Rev. Cancer. 2007; 7(10): 750-62.

20. Greiner TC, Moynihan MJ, Chan WC, Lytle DM, Pedersen, Anderson JR, et al. P53 Mutations in Mantle Cell Lymphoma Are Associated With Variant Cytology and Predict a Poor Prognosis. Blood. 1996; 87(10): 4302-10.

21. Allen JE, Bottomley S, Alcock HE, Baird M, Hammond DW, Hough RE, et al. Identification of novel regions of amplification and deletion within mantle cell lymphoma DNA by comparative genomic hybridization. British Journal of Haematology. 2002; 116(2): 291-8.

22. Walsh SH, Thorsélius M, JohnsonA, Söderberg O, Jerkeman M, Björck E, et al. Mutated VH genes and preferential VH3-21 use define new subsets of mantle cell lymphoma. Blood. 2003; 101(10): 4047-54.

23. Bertoni F, Rinaldi A, Zucca E and Cavalli F. Update on the molecular biology of mantle cell lymphoma. Hematological Oncology. 2006; 24(1): 22-7.

24. Delfau-Larue MH, Klapper W, Berger F, Jardin F, Briere J, Salles G, et al. High-dose cytarabine does not overcome the adverse prognostic value of CDKN2A and TP53 deletions in mantle cell lymphoma. Blood. 2015; 126(5): 604-11.

25. Nagy B, Lundán T, Larramendy ML, Aalto Y, Zhu Y, Niini T, et al. Abnormal expression of apoptosis-related genes in haematological malignancies: Overexpression of MYC is poor prognostic sign in mantle cell lymphoma. British Journal of Haematology. 2003; 120(3): 434-41.

26. Cuneo A, Bigoni R, Rigolin GM, Roberti MG, Bardi A, Piva N, et al. Cytogenetic profile of lymphoma of follicle mantle lineage: correlation with clinicobiologic features. Blood. 1999; 93(4): 1372-80.

27. Rinaldi A, Kwee I, Taborelli M, Largo C, Uccella S, Martin V, et al. Genomic and expression profiling identifies the B-cell associated tyrosine kinase Syk as a possible therapeutic target in mantle cell lymphoma. British Journal of Haematology. 2006; 132(3): 303-16.

28. Kridel R, Meissner B, Rogic S, Boyle M, Telenius A, Woolcock B, et al. Whole transcriptome sequencing reveals recurrent NOTCH1 mutations in mantle cell lymphoma. Blood. 2012; 119(9): 1963-71.

29. Hofmann WK, De Vos S, Tsukasaki K, Wachsman W, Pinkus GS, Said JW, et al. Altered apoptosis pathways in mantle cell lymphoma detected by oligonucleotide microarray. Blood. 2001; 98(3): 787-94.

30. Barna G, Reiniger L, Tátrai P, Kopper L, and Matolcsy A. The cut-off levels of CD23 expression in the differential diagnosis of MCL and CLL. Hematological Oncology. 2008; 26(3): 167-70.