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Review Article

Pathology and Diagnosis of Mantle Cell Lymphoma

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ARTICLE INFO

Article history:

Received: 29 May, 2020

Accepted: 10 June, 2020

Published: 16 June, 2020

Keywords:

Mantle cell lymphoma

cyclin D1

cytogenetic

molecular diagnosis

pathology

ABSTRACT

Mantle Cell Lymphoma (MCL) is a rare type of B-cell non-Hodgkin lymphoma (NHL), characterised by an aggressive clinical course and a poor prognosis that remains incurable for the majority of patients. Cyclin D1 overexpression, which results from t(11; 14)(q13; q32), is the pathogenic hallmark in MCL disease and causing cell cycle disruption. MCL has been categorized based on lymphoid malignancies in the WHO update into two significant subgroups, nodal and leukemic non-nodal MCL; each type has a particular clinical presentation and distinct molecular features. SOX11 is overexpressed in nodal MCL subtype, while the leukemic non-nodal sub-type is associated with SOX11 negativity. MCL has a wide range of differential diagnoses, including other types of low-grade lymphoma, most notably chronic lymphocytic leukaemia (CLL), follicular lymphoma (FL), marginal zone lymphoma (MZL), and lymphoblastic lymphoma (LBL). Therefore, accurate histological biopsy diagnosis is paramount in this rare subtype of NHL. MCL has a distinctive clinical presentation and particular morphological and immunophenotypic features with specific cytogenetic abnormalities. The recent advances in molecular and cytogenetic analysis have improved the accuracy of MCL diagnosis and enhanced disease prognosis. Furthermore, B cell receptor inhibitors have revolutionized MCL treatment. Therefore, an accurate diagnosis of MCL is very important since this may require an aggressive and novel targeted therapy.

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Introduction

Mantle Cell Lymphoma (MCL) is a rare type of non-Hodgkin lymphoma (NHL), with an aggressive clinical course. However, a minority of patients will not require any treatment for many years [1, 2]. Treatment of MCL usually associated with short-lived transit response to chemotherapy. MCL is associated with poor prognosis and incurable disease in the majority of patients. The median age at diagnosis is 65 years, and advanced-stage disease at diagnosis is the common presentation for MCL patients (70%). Generalised lymphadenopathy is the common clinical presentation (75%), while extranodal disease accounts for 25% [3]. Common sites of involvement include the lymph nodes, spleen (45-60%), Waldeyer's ring, bone marrow (>60%), blood (13-77%), and extranodal sites, such as the gastrointestinal tract, breast, pleura, and orbit [4, 5]. Although MCL is initially responsive to different conventional chemotherapies, such response is short-lived.

The most commonly used prognostic scoring system is the Mantle cell lymphoma International Prognostic Index (MIPI) and this is used to predict which patients will have a more aggressive clinical course [6]. The WHO 2016 update of lymphoid malignancies has categorized MCL into two subgroups, nodal and leukemic non-nodal MCL, which differ in the clinical presentations and molecular features [7]. Therefore, accurate histological biopsy diagnosis is paramount in this rare subtype of NHL.

Pathology of Mantle Cell Lymphoma

I Pathogenesis

The pathogenic hallmark in MCL is overexpression of Cyclin D1, which results from the t (11; 14) (q13; q32) translocation [8]. The classical

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(nodal) MCL is believed to arise from naïve centre B cells (pre-germinal) of the mantle zone and mostly show SOX11 expression and usually involves lymph nodes and extranodal sites, for example, 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 either from peripheral blood memory B cells or from marginal zone cells. It mainly involves the peripheral blood, spleen, and bone marrow and is most often clinically indolent, not requiring treatment.

II Morphology

The histologic growth pattern of MCL in lymph nodes is variable, and it could nodular, diffuse or involve the mantle zone, or a combination of these patterns. The most common pattern is an infiltrate mainly composed of small to medium-sized B lymphocyte, with notched nuclei and inconspicuous nucleoli. However, the morphology can range from small, more irregular lymphocytes to immature looking cells (in the blastoid variant) and even occasionally a combination of both of small and large cells or markedly atypical large cells (in the pleomorphic variant) [9, 10]. When malignant effusions are present, the tumor cells usually with similar morphology of peripheral blood.

III Immunophenotype

MCL cells usually show high expression of surface IgM (sIgM) and IgD, the majority of cases (80%) with lambda light chain restriction. Pan B-cell antigen markers (e.g., CD19, CD20) are positive also CD5, and FMC7. While CD23 expression is dim or negative as CD200 and with a strong Cyclin D1 expression. CD5– or CD23+ has been reported in rare cases [11].

i Cyclin D1

Up to 95% of MCL biopsy showed intense nuclear staining of overexpressed Cyclin D1 on immunohistochemical analysis of both nodal/extranodal tissues. This is not expressed on normal B-lymphocytes [12]. A translocation between the CCND1 locus and the immunoglobulin heavy chain (IgH) locus, t(11; 14)(q13; q32), this led to overexpression of Cyclin D1, which is involved in the control of the G1 phase of the cell cycle, in most of MCL cases [13, 14]. However, the t(11; 14) is not specific to MCL, and it occurs in multiple myeloma (30%), and rarely seen in other types of lymphomas [15]. This translocation is seen in about 50% of the patients on conventional cytogenetics, but fluorescence in situ hybridization (FISH) will have a higher percentage of positivity [16]. Cyclin D1 overexpression is useful to differentiate MCL from other relatively indolent B cell lymphomas, such as CLL / SLL, FL, LBL, and splenic MZL [17]. Cyclin D1 may be overproduced even in cases lacking the t(11; 14), suggesting that other types of acquired genetic aberrations. No difference was noted between Cyclin D1 positive and negative MCL when gene expression profiling was used. In Cyclin D1 negative cases, instead, either Cyclin D2 or D3 is overexpressed, which are highly homologous and functionally identical to Cyclin D1, and no difference in clinical behaviour or outcome was observed [18].

ii SOX11

It is a transcription factor which is not typically expressed in normal B cells and rarely expressed in other lymphoid neoplasms [7]. It is overexpressed 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 [19]. SOX11 expression is also a useful marker MCL, particularly in rare cases that do not express Cyclin D1 development. The prognostic impact of SOX11 expression in MCL is not well-described; overexpression of SOX11 appears to be associated with a worse prognosis even in cases of Cyclin D1 negative and Cyclin D2 negative MCL [20, 21].

IV Genetic Features

MCL is known to have the highest genomic instability among B cell malignancies and a significant number of secondary chromosomal alterations have been described [22]. *TP53* mutation, in particular, which is 15-20% more common in the blastoid variant and associated with a dismal prognosis in MCL with a median survival of 1.3 years versus 5.1 years for non-mutated disease ($p=0.023$) [23]. In contrast, the prognostic relevance of 17p deletion in MCL is less described, although some reports indicated an association with poor prognosis [24].

Both immunoglobulin (Ig) heavy and light chain genes are rearranged in MCL. The Ig V region genes lack somatic mutations in most cases, indicating a pre-germinal center stage of differentiation, consistent with an origin from an immunologically naïve mantle zone B cells [25, 26]. Karyotyping of metaphase chromosomes could detect t(11; 14) in only 50-65 % of MCL cases, but by fluorescence in situ hybridization (FISH) a much higher fraction of cases with Cyclin D1 overexpression contain CCND1/IgH fusion genes [27]. Other genes associated with the cell cycle may also be expressed abnormally, including the 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 [21, 28]. The acquisition of a translocation involving the oncogene MYC has been associated with shorter survival [29]. Additional genomic alterations in *TP53*, p16, p18, p21, and p27 have been reported to play a role in MCL development and evolution [30]. The 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 [31, 32]. Other studies have identified activating NOTCH1 mutations in a minority of MCL cases, a finding that may predict a worse clinical outcome [32]. additional work is needed to confirm this association. Deletion of or point mutations in the ATM tumor suppressor gene (11q22-q23) are seen in 30-50% of MCL cases [33]. Microarray studies have suggested that MCL cases display disturbances of pathways associated with apoptosis [34]. Specifically, MCL cells appear to avoid programmed cell death (apoptosis) by the expression of BCL2, upregulation of the PI-3 kinase/AKT pro-survival signalling pathway, activation of nuclear factor- κ B (NF- κ B), and mutations in *TP53*. Inhibitors for these pro-survival signalling pathways have revolutionized MCL treatment.

Differential Diagnosis

MCL has a wide range of differential diagnosis, such as other NHL with small and medium sized cells, most notably CLL / SLL, FL, MZL and LBL. Both MCL and CLL are composed of small to medium-sized B lymphocytes and share similar immunohistochemistry profile. While CLL is positive for CD5, CD20, and CD23, MCL is positive for CD5 and CD20 but negative for CD23.

Cyclin D1 expression on immunohistochemistry 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 [35]. MCL with a predominant nodular growth pattern on histology may resemble that of follicular lymphoma. However, in contrast to follicular lymphoma, MCL cells are usually CD5, CD43 and Cyclin D1 positive and CD10 negative. Like MCL, follicular lymphoma can present with gastrointestinal involvement as lymphomatous polyposis; such tumors are also best distinguished from MCL by immunohistochemistry.

Both extranodal MZL and MCL can involve the gastrointestinal tract and are neoplasms characterised by small to medium-sized B lymphocytes. On immunophenotype, MCL expresses CD5 and Cyclin D1 while extranodal MZL does not. Also, MZL often contains monocytoid B cells and shows plasmacytic differentiation, which is not the features of MCL.

The mitotic rate measured by Ki67 expression is usually high in the blastoid variant of MCL, which often comprised of intermediate-sized malignant lymphocytes with dispersed chromatin, irregular nuclear borders, 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. In contrast, 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 rare type of NHL with unique clinical and pathological features and a characteristic cytogenetic abnormality, the t(11; 14)(q13; q32). This tumor generally carries a dismal prognosis and requires an aggressive and novel therapy; therefore, an accurate diagnosis of MCL is of great importance. In contrast, the indolent leukemic variant MCL should be considered for observation. There is a wide differential diagnosis for MCL and morphologic findings that can be misinterpreted as other types of NHL. The molecular basis of MCL highlights the biologic role as diagnostic and prognostic aids and as targetable by novel therapies.

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