Mantle cell lymphoma

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Abstract

Mantle cell lymphoma (MCL) is a B-cell neoplasm that usually carries the t(11;14)(q13;q32) translocation and constitutively overexpresses cyclin D1. The clinical evolution is relatively aggressive with a poor response to conventional therapeutic regimens, frequent relapses and a median overall survival of 3.5 years. MCL has a wide spectrum of growth patterns. Most cases have a vaguely nodular and/or diffuse growth pattern, very rare cases have a follicular growth pattern, and a larger minority has a mantle zone growth pattern in which the lymphoma grows as an expanded ring around reactive germinal centers. “In situ MCL” is considered as a very early stage of MCL or even a pre-neoplastic state, and thought to be the tissue equivalent of clonal circulating cells carrying the genetic alterations found in their overt counterpart lymphomas. These are mainly incidental findings, and are defined as lesions that remain compartmentalized (germinal centre/mantle zone) without altering the normal/reactive lymph node (LN) architecture. (Hsu, et al. 2014. Cortelazzo, et al. 2012).

Phenotype/cell stem origin

The postulated normal counterpart of MCL is peripheral B-cell of inner mantle zone, mostly of naïve pre-germinal center type (Swerdlow, et al, 2008).

MCL expresses CD20, PAX5, CD43, bcl2, and usually positive for CD5, cyclinD1, but there are minority of cases are negative for CD5, cyclinD1. Sox11 can express in cyclinD1 negative cases. Rare MCL are negative for cyclin D1 and the t(11;14) but have an expression profile and other features indistinguishable from conventional MCL, which have a high expression of cyclinD2 or cyclinD3. MCL is negative for CD10 and bcl6 (Swerdlow, et al, 2016).

Clinics and pathology

Disease


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Mantle cell lymphoma

al. 2008. Swerdlow, et al, 2016). Aberrant phenotypes have been described, sometimes in association with blastoid/pleomorphic variants; these variants include negativity for CD5 (12% of cases), and positivity for CD10 (8%), CD23 (21%), bcl-6 (12%), and MUM1 (35%). (Cortelazzo, et al. 2012).

Epidemiology

The incidence of MCL is about 3-10% of non-Hodgkin lymphoma. It occurs in middle-aged to older individuals with a median age about 60 and a variably marked male predominance (about 2:1 or greater) (Swerdlow, et al, 2008. Swerdlow, et al, 2016).

Bermudez et al studied a series of 341 consecutive lymph node resection specimens from patients diagnosed with colorectal and breast adenocarcinoma and incidental and isolated MCLIS was found in 2/341 patients(0.59%). (Bermudez, 2016).

Clinics

Lymph nodes are the most commonly involved site; the spleen and bone marrow, with or without peripheral blood (PB) involvement, are other important sites of disease. Other extranodal sites are frequently involved, including the gastrointestinal tract and Waldeyer ring. Most cases of multiple lymphomatous polyposis represent MCL (Swerdlow, et al, 2008. Swerdlow, et al, 2016).

Pathology

Morphologically, classical MCL is a monomorphic lymphoid proliferation with a vaguely nodular (13%), diffuse (61%), mantle zone (26%) or rarely follicular growth pattern. Most cases are composed of small to medium-sized lymphoid cells with slightly to markedly irregular nuclear contours, most closely resembling centrocytes. The nuclei have at least somewhat dispersed chromatin but conspicuous nucleoli. Hyalinized small vessels and scattered single epithelioid histiocytes are commonly seen.

Evaluation of the proliferation fraction either by counting mitotic figures or estimating the proportion of Ki67 positive nuclei is important for prognosis. The proliferation activity may vary in different cases, but it is generally low, with a percentage of Ki-67 positive cells around 15-30%. In blastoid variant there is a high proliferative activity (Ki-67 positive cells > 40%) (Swerdlow, et al. 2008. Swerdlow, et al, 2016. Cortelazzo, et al. 2012).

There are some variants of MCL: blastoid and pleomorphic variant (aggressive), and small cell, marginal zone-like variant.

Blastoid variant: loss of a mantle zone growth pattern, increase in nuclear size and mitotic activity, cells resemble lymphoblasts with dispersed chromatin and a high mitotic rate (usually at least 20-30/10HPF).

Pleomorphic variant: cells are pleomorphic but many are large with oval to irregular nuclear contours, generally pale cytoplasm and often prominent nucleoli in at least some of the cells.

Small cell variant: small round lymphocytes with more clumped chromatin, either admixed or predominant, mimicking a small lymphocytic lymphoma.

Marginal zone-like variant: prominent foci of cells with abundant pale cytoplasm resembling marginal zone of monocytoid B-cell mimicking a marginal zone lymphoma; sometimes these paler foci may also resemble proliferation centers of chronic lymphocytic leukaemia/small lymphocytic lymphoma.

‘In situ’ MCL shows involvement almost exclusively restricted to the inner mantle zones or to narrow mantles, consisting of cyclin D1+ cells typically in the inner mantle zones of follicles in the absence of overt lymphoma. The mantle zones appear normal or only mildly expanded. In many cases, this is an incidental finding, though can be found in the presence of other small B cell lymphomas or overt MCL. In 2016 WHO classification, ‘in situ MCL’ is renamed as in situ mantle cell neoplasia (ISMN) to distinguish it from overt MCL, and can be considered observation in patients with indolent disease (asymptomatic with low Ki67 or leukemic non-nodal disease) (Lynch, et al. 2017). These cases must be distinguished from mantle cell lymphoma with a mantle zone pattern and overt mantle cell lymphoma because they may not require therapeutic intervention Carvajal-Cuenca, 2012).
Mantle cell lymphoma

Two subtypes of MCL based on different clinicopathological features and molecular abnormalities are recognized: classical MCL and leukemic non-nodal MCL. 'leukemic' non-nodal MCL (previously mistaken for CLL) is a distinct variant which is associated with hyper-mutated IGHV, no expression of SOX11, low Ki67, and few or no other molecular abnormalities beyond a t(11;14) translocation. It typically has an indolent clinical course, infrequent peripheral lymphadenopathy, but is commonly associated with splenomegaly, bone marrow, and peripheral blood involvement (limited to blood and bone marrow) (Lynch, et al. 2017. Ondrejka, et al, 2011).

Figure 1. Mantle cell lymphoma. Diffuse architectural effacement can be seen, composed of small to medium-sized lymphoid cells. (HE staining).

Figure 2. Mantle cell lymphoma, blastoid variant. The lymphoid cells are medium in size, resembling lymphoblasts with dispersed chromatin and a high mitotic rate. (HE staining).
Mantle cell lymphoma

Figure 3. The cells are positive for CD20.

Figure 4. The cells are positive for CD5.

Figure 5. The cells are positive for cyclinD1.
Mantle cell lymphoma

Figure 6A. Mantle cell lymphoma, 'in situ'. Morphology reveals a lymph node with multiple reactive-appearing follicles and prominent paracortical hyperplasia (HE staining).

Figure 6B. Higher power view of one reactive-appearing follicles with germinal centers and normal mantle zones (HE staining).

Figure 6C. The mantle zone cells are positive for CD20.
Figure 6D. The cells are positive for CD5 with numerous T-cells in paracortical regions.

Figure 6E. The cells are positive for cyclin D1 highlighting scattered positive cells in mantle zones.

Figure 6F. The proliferation index of Ki67 is low in mantle zone cells.
**Treatment**

MCL has a median survival of 3-5 years with a short remission duration to standard therapies, but the vast majority of patients cannot be cured. The impact of some of the newer therapeutic approaches remains to be established. (Swerdlow, et al. 2008. Swerdlow, et al. 2016). For selected indolent (either low tumor burden/low proliferative index nodal form or leukemic non-nodal form are often asymptomatic and can be observed with favorable long-term outcomes), low MIPI MCL patients, initial observation may be appropriate therapy. For younger patients with intermediate or high risk MIPI MCL, aggressive therapy with a cytoreductive containing regimen autologous stem cell transplantation should be considered. For older MCL patients with intermediate or high risk MIPI, combination chemotherapy with R-CHOP, Rituximab, or a clinical trial should be considered. At the time of relapse, agents directed at activated pathways in MCL cells such as bortezomib (NFkB inhibitor), BTK inhibitors or CAL-101 (B-cell receptor inhibitors) or lenalidamide (anti-angiogenesis) have clinical activity in MCL patients. Autologous or allologeneic stem cell transplantation can also be considered in young patients. (Vose, 2012. Vose, 2015. Vose, 2017).

It is important to recognize that ISMN does not represent a lymphoma diagnosis and no additional evaluation or therapy is warranted. (Lynch, et al. 2017)

MCL is heterogeneous a disease, and so are the people that have it; although guidelines are appropriate, therapeutic approaches must be individualized based on a variety of factors and need for personalized therapy to ensure optimal outcomes. (Martin, et al. 2017. Sandoval-Sus, et al.2017). Targeted strategies include the proteasome inhibitors, immune modulatory drugs (IMiDs), mammalian target of rapamycin (mTOR) inhibitors and especially inhibitors of the B-cell receptor pathway (Dreyling, 2015). Given the excellent OS rates regardless of initial therapy in patients with early-stage MCL, de-intensified therapy to limit treatment-related toxicity is a reasonable approach (Dabaja, 2017).

**Prognosis**

The most consistently reported adverse histopathological prognostic parameter is a high mitotic rate. A high proliferation index of Ki67 is an adverse prognostic indicator. Some studies reported adverse prognostic features includes: blstoid/pleomorphic morphology, trisomy 12, karyotypic complexity, TP53 mutation/overexpression/loss and overt PB involvement, gains of chromosome 3q and deletions of 9q. The small cell variant and 'in situ' MCL appear to have better course. (Swerdlow, et al. 2008. Swerdlow, et al. 2016). The absence of SOX-11 or a low Ki-67 may correlate with a more indolent form of MCL. The MCL international prognostic index (MIPI) is the prognostic model most often used and incorporates ECOG performance status, age, leukocyte count, and lactic dehydrogenase. A modification of the MIPI also adds the Ki-67 proliferative index if available (Vose, 2012. Vose, 2015. Vose, 2017). The use of intensive frontline therapies including rituximab and consolidated by ASCT ameliorates response rate and prolongs progression-free survival, but any impact on survival remains to be proven. The development of targeted therapies as the consequence of better dissection of pathogenetic pathways in MCL might improve the outcome of conventional chemotherapy in most patients and spare the toxicity of intense therapy in a minority of MCL patients characterized by a relatively indolent disease (Cortelazzo, et al. 2012).

The ‘in situ MCL’ is associated with incidental finding, indolent clinical course and lower tumor burden. (Hsu, et al. 2014)

**Genetics**

Immunoglobulin genes are rearranged. Variable region genes are unmutated in the majority of the cases, but in 15-40% of the cases, IG genes show somatic hypermutation. The t(11;14)(q13;q32) between IGH and cyclinD1 (CCND1) genes is present in almost all cases and considered the primary genetic event. Inactivating mutations of the ATM gene at 11q22-23 have been detected in 40-75% of MCL. (Swerdlow, et al. 2008. Swerdlow, et al. 2016). MCL represents the lymphoma subtype with the highest number of cytogenetic alterations. Secondary chromosomal aberrations including gains in 3q26(31-50%), 7p21 (16-34%) and 8q24 (16-36%; MYC) as well as losses of 1p 13-p31 (29-52%), 6q23-27 (23-38%), 9p21 (18-31%), 11q22-23 (21-59%), 13q11-q13 (22-55%), 13q14-q34 (43-51%) and 17p13pter (21-45%) has been reported. Trisomy 12 was found in 25% of cases. (Cortelazzo, et al. 2012). One study identified a functional LINC-ROR (lncRNA ROR-AS1) involved with regulation of gene transcription via associating with PRC2 complex, and may serve as a novel biomarker in MCL patients. (Hu, et al. 2017) There is also improved understanding of the molecular abnormalities seen in MCL, with alterations in ATM, cyclin D1, NOTCH1, and NOTCH2 being more common. (Lynch, et al. 2017).

The t(11;14) was demonstrated in nine of nine cases with an 'in situ MCL' pattern of cyclin D1-positive cells by conventional cytogenetics of lymph node or peripheral blood samples (3 cases) and/or by FISH studies (8 cases) (Carvajal-Cuenca, 2012).
Cytogenetics

Cytogenetics morphological

\( t(11;14)(q13;q32) \) IGH/CCND1

Genes involved and proteins

**CCND1**

**Location**

11q13.3

**DNA/RNA**

5 exons.

**Protein**

CCND1 binds and activates the G1 cyclin dependent kinases, CDK4 and CDK6. CDK-cyclin D complex phosphorylates members of the retinoblastoma protein family. Regulates the G1/S transition in the cell cycle. Essential for G1 progression. Promotes cellular proliferation and block cell differentiation. Found involved in translocations with fusion genes, amplified or over-expressed, or mutated in a number of cancers.

**IGH**

**Location**

14q32.33

**References**


This article should be referenced as such:


