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Lymphoma (DO Persky, Section Editor)

Leukemic Non-nodal Mantle Cell Lymphoma: Diagnosis and Treatment

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Opinion statement

Mantle cell lymphoma (MCL) encompasses nearly 6% of all the non-Hodgkin lymphomas. It is considered an incurable neoplastic process arising from B cells. The cytogenetic abnormality t(11;14) (q13; q32) leading to cyclin D1 overexpression is the sentinel genetic event and provides an exceptional marker for diagnosis. MCL is generally considered to have an aggressive course as compared with other indolent lymphomas with traditionally reported median survival of 3–5 years. According to the 2016 WHO classification, there are two major known variants of MCL: classical which affects the lymph nodes and extra nodal sites and leukemic non-nodal MCL (L-NN-MCL) which characteristically involves the bone marrow, peripheral blood, and the spleen. It is important to distinguish between classical and leukemic non-nodal MCL since the latter variant of MCL follows a rather indolent course with a wait and watch approach in order to avoid overtreatment. However, a subset of patients with L-NN-MCL can transform into a more aggressive course requiring treatment. Current evidence suggests those patients with alteration in TP53

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gene do not respond to standard chemotherapy agents and may need targeted therapy. In this review, we describe the characteristics of L-NN-MCL, its diagnosis, and management.

Introduction

Mantle cell lymphoma (MCL) makes up approximately 6% of all the non-Hodgkin lymphomas [1]. It is a malignancy of B cells and generally considered to be an incurable neoplastic process arising from the mantle zone of the lymph node. It presents most commonly with generalized lymphadenopathy, hepatosplenomegaly, and extra nodal disease which principally involves the bone marrow and gastrointestinal tract [2, 3]. The cytogenetic abnormality t(11;14)(q13; q32) leading to cyclin D1 overexpression is the chief genetic event and provides an exceptional marker for diagnosis. In a few cases where cyclin D1 staining is negative, SOX11 can help establish the diagnosis [4]. MCL cells traditionally express CD5 and cyclin D1 while lacking CD10, CD23, and Bcl6 expression [5]. This aggressive lymphoma is also known to accumulate a large number of chromosomal aberrations that principally target genes that are responsible for cell survival pathways and DNA damage response [6]. MCL has been thought to have a relatively more aggressive clinical course compared with other indolent lymphomas. Traditionally, the reported median survival of MCL is about 3–5 years, but this is changing with the emergence of modern management approaches.

Pathology and diagnosis of MCL

According to the 2016 World Health Organization (WHO) classification, two major known variants of MCL have been recognized, the classical type which involves the lymph nodes and extra nodal sites, and leukemic non-nodal MCL (L-NN-MCL) type which characteristically involves the bone marrow, peripheral blood, and the spleen [2, 3]. A range of other morphological variants of MCL have been described which may lead to diagnostic uncertainty, including small cell variants which mimic small lymphocytic lymphoma, marginal zone variant, and blastoid and pleomorphic variants which mimic aggressive lymphomas [4]. Table 1 depicts some differences between classical MCL and L-NN-MCL.

Table 1. Differences in the L-NN-MCL and cMCL

Variable	L-NN-MCL	cMCL
Mutated IGHV	More common	Less common
Involvement of bone marrow	More common	Less common
LDH	Low	High
Poor performance status (ECOG > 1)	Rare	Common
IG light chain restriction	Kappa	Lambda
Rate of proliferation	Low	High

L-NN-MCL, leukemic non-nodal mantle cell lymphoma; *cMCL*, classical MCL; *LC*, light chain; *IG*, immunoglobulin; *LDH*, lactate dehydrogenase; *ECOG*, Eastern Cooperative Oncology Group; *PS*, performance score

To aid in the stratification of patients with MCL, various prognostic biomarkers have been proposed [4]. These markers include baseline clinical aspects (MIPI (Mantle Cell International Prognostic Index)), leukemic non-nodal and in-situ presentation; pathological aspects (blastoid morphology, Ki-67 proliferation index), SOX11 expression; genetic aspects (Ig mutation status, TP53, CDKN2A deletion); and depth of response after the treatment (positron emission tomography (PET) and mismatch repair deficiency (MMRD)). These tools help identify appropriate management strategy for patients presenting with this disease. Specifically, with respect to L-NN-MCL, a watchful waiting approach has been proposed for the patients as they often present with favorable prognostic features and have better outcomes than classical MCL. L-NN-MCL tends to present with a lower MIPI/Ki-67 proliferation rate, lack of SOX 11 expression, and mutated Ig genes demonstrating their generally less aggressive feature [4].

A thorough radiological staging (computed tomography (CT) or when available PET/CT scan) to demonstrate the absence of significant lymphadenopathy is required for the diagnosis of leukemic non-nodal MCL variant. Additionally, patients with gastrointestinal symptoms need a full endoscopic study to establish or exclude extra nodal involvement [4]. It should be noted that many of the patients with classical MCL have circulating lymphoma cells during the disease course. However, these patients are not considered leukemic non-nodal MCL, as they have concurrent lymphadenopathy.

Ye et al. [7] proposed the term "smoldering" MCL to encompass all types of MCL which are indolent in behavior and the "wait and watch" approach can be used for their management. The authors reported that the absence of B symptoms, a normal lactate dehydrogenase (LDH) and beta-2-microglobulin level, low MIPI score, spleen size < 20 cm, maximum tumor diameter less than 3 cm, PET/CT with standard uptake value max < 6, Ki-67 < 30%, cluster of differentiation (CD) 5, CD38 negative, increased CD23-positive lymphocytes, increased CD200 expression, kappa light chain restriction, absence of C-myc, tumor protein (TP) 53 and NOTCH1/2 mutations, no tumor growth on re-evaluation, and non-blastoid/pleomorphic morphology are the characteristics defining the smoldering form of MCL. Their proposed classification is shown in Fig. 1 [7].

Leukemic non-nodal MCL (L-NN-MCL) variant

The L-NN-MCL is considered a distinct clinical entity within MCL. Vizcarra et al. [8] were the first to report the concept of the two subgroups (i.e., classical and L-NN-MCL variants) with distinct clinical and biological features in 2001. Subsequently, cases of indolent MCL were reported by Nodit et al. [9] (2003) and Espinet et al. [10] (2005). L-NN-MCL shows a less aggressive clinical course in comparison with the classical MCL [11], and thus, sometimes managed with a "wait and watch" approach or with treatment approaches that are much less intensive [12, 13]. The important consideration is to identify the subset of patients who have a more aggressive form and tailor therapy [14•].

L-NN-MCL shares a few similar genetic features with MCL but also has its own unique features including mutated IgVH (immunoglobulin heavy chain genes), decreased cell adhesion/invasion property, and reduced expression of SOX11 gene and CD23 expression [15, 16, 17•]. Therefore, SOX11 can serve as a biomarker for the diagnosis and prognosis of a subset of MCL patients.

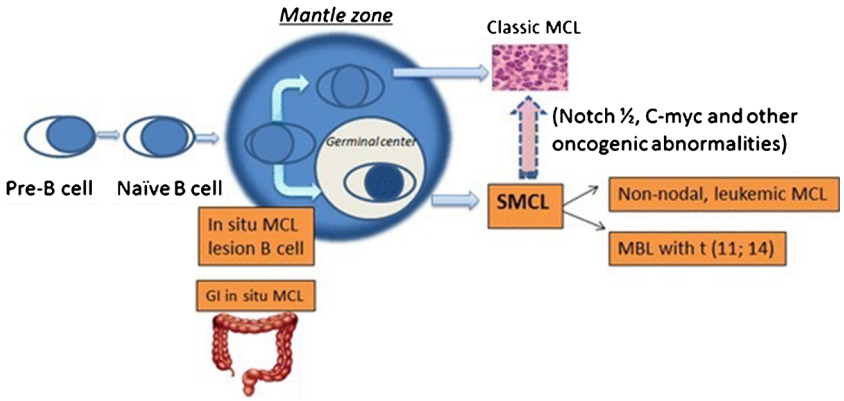

Fig. 1. Schematic illustration showing two forms of mantle cell lymphoma (MCL) as initially proposed by Ye et al. [7], classic MCL and smoldering MCL. Reproduced from Ye et al., smoldering mantle cell lymphoma. *J Exp Clin Cancer Res.* 2017;36 (1):185, which is distributed under the terms of the Creative Commons Attribution 4.0 International License (https://creativecommons.org/licenses/by/4.0/).

Additionally, ataxia-telangiectasia mutated (ATM), cyclin-dependent kinase (CDK) N2A, and chromatin modifier genes, such as *MLL2*, *WHSC1*, and *MEF2B*, are frequently mutated in the SOX11-positive tumors whereas these mutations are not seen in tumors that are SOX11 negative [18]. Two major genetic and molecular pathways (Fig. 2) have been identified in the pathogenesis of L-NN-MCL which has been identified to be both clinically and biologically different from the conventional SOX11-positive MCL. Constitutive deregulation of cyclin D1 and early expansion of malignant B cells in the mantle zone

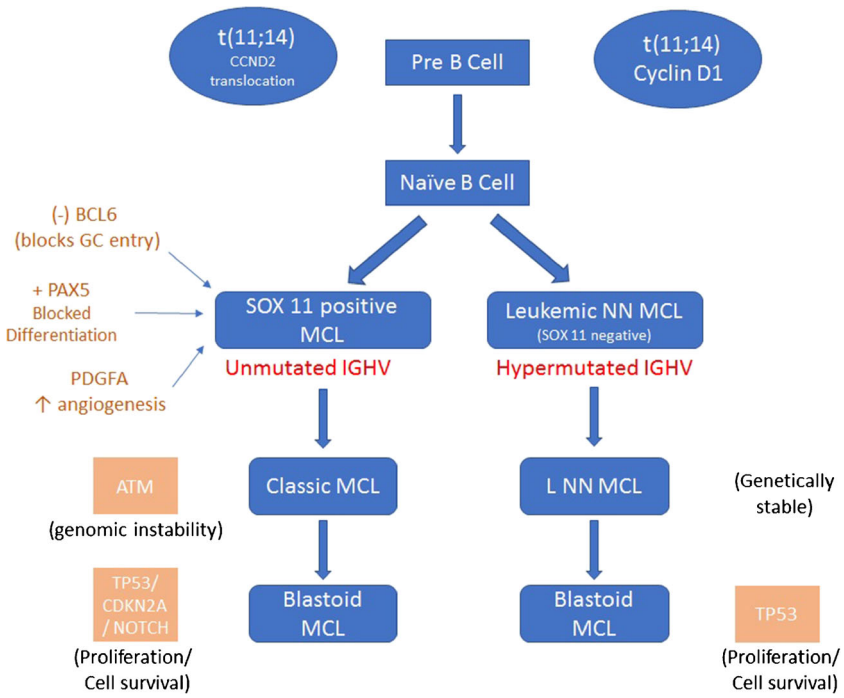

Fig. 2. Showing pathogenesis and differences between the SOX11-positive and SOX11-negative mantle cell lymphoma (MCL).

of lymphoid follicles occurs through t(11;14) translocation in an immature B cell in both subtypes of MCL [19–21]. Rarely, some tumors have CCND2 translocation with SOX11 expression in the absence of t(11;14) [22]. G1 cyclin overexpression leads to MCL development by overcoming the cell-cycle suppressor effect of retinoblastoma and p27 proteins [23, 24]. SOX11-positive MCL more commonly expresses unmutated IGHV and may be acquired from the cells that have not encountered the impact of the germinal center microenvironment [25]. SOX11 may promote tumor development by hindering terminal B cell differentiation and coercing PAX5 expression, reducing BLIMP1 and XBP1 expression, and thus, halt its downregulation which is essential for plasma cell differentiation [26].

Infiltration of tissues by the tumor cells is augmented by the expression of platelet-derived growth factor A chain (PDGF-A), which is an angiogenic factor promoted by SOX11 [27]. More aggressive variants of MCL present more frequently with ATM mutations, which lead to the development of auxiliary genetic alterations, augmented genomic instability, and further variation in cell cycle and cell survival regulatory genes while hypermutated IGHV is seen in L-NN-MCL [18]. These tumors are genetically stable and persevere with a leukemic phase for a long time and may also present with splenomegaly. In the course of the disease, additional genetic alterations may ensue, such as TP53 inactivation, which may cause disease transformation [18].

Diagnosis

The diagnosis of L-NN-MCL and its differentiation from classical MCL, as previously described is important. Genetic variation between the classical and non-nodal MCL can help aid the diagnosis. In a study on 80 patients with circulating t(11;14) lymphocytes, Orchard et al. [11] found that 37 out of 40 patients presented without lymphadenopathy (non-nodal group). A significantly higher number of patients belonging to the non-nodal group showed IGVH mutation and CD38 negativity [16]. In another case series conducted in 2005 by Rubio-Moscardo et al. [26], 11 of 68 patients (16%) were classified as leukemic MCL, whereas 57 patients had lymph node involvement. The authors reported that the non-nodal cases were different from the nodal MCL in terms of lacking lymphadenopathy and having marked lymphocytosis (8.8 × 10 [9]/L to 50 × 10 [9]/L). Additionally, the non-nodal cases showed a different genetic profile from nodal cases including frequent deletion of 8p21.3 at the tumor necrosis factor (TNF)-related apoptosis-inducing ligand (TRAIL) receptor gene cluster (55% vs 19%;), gain of 8q21.1 at the MYC gene locus (47% vs 14%;), and more frequent IGVH mutation (64% vs 21%) [28].

Royo et al. [15] in their study of 42 patients with L-NN-MCL and 68 classical MCL noted that all cases (both classical and L-NN-MCL) overexpressed cyclin D1. The authors studied the signature of SOX11, HDGFRP3, and DBN1 (3 gene signature) and found that the non-nodal MCL variant was negative for this 3 gene signature. The authors also found that IGHV gene was mutated in 77% of the tumors in L-NN-MCL when compared with only 17% cases with the classical MCL [14•]. Patients with non-nodal presentation in combination with low signature had an improved outcome (5-year overall survival (OS) 86%, 95% confidence interval (CI), 67–100) when compared with the patients with

non-nodal disease with high signature (5-year OS 42%, 95% CI, 1–83), and patients with nodal presentation had a worse outcome irrespective of the signature expression [14•].

Aggressive form of L-NN-MCL

A few cases of L-NN-MCL can transform from an indolent disease to a more aggressive form of disease which may present with cytopenias and/or symptoms including but not limited to fatigue or weight loss due to splenomegaly. Questions have been raised as to the recognition of specific biological markers and characteristics that can aide in distinguishing the aggressive form of L-NN-MCL to help in avoiding over-treatment. Royo et al. [15] reported that a subgroup of patients from the non-nodal L-NN-MCL group progressed more rapidly despite a low 3 gene signature. The authors suggested that evaluation of 17p/TP53 alterations might be important to recognize this aggressive form of L-NN-MCL [14•].

Chapman-Fredricks et al. [27] reported three patients with L-NN-MCL with mutations in TP53, ATM, and/or 13q14 deletion. All the three patients were found to have disease progression. Two out of the three patients had to undergo treatment at 5 and 18 months after the initial presentation. The third patient also showed progression but was lost to follow-up [29••].

Treatment

Most cases of L-NN-MCL can be managed with the "wait and watch" approach as mentioned above, especially patients with good prognostic factors. In their study on 80 patients with circulating t(11;14) lymphocytes, Orchard et al. [11] found that a significantly lower number of patients in the non-nodal group required immediate treatment and showed better survival compared with the nodal group [16].

It is well established that p53 mutation is a harbinger of more aggressive disease, and it has been shown in a study on 50 MCL patients to confer resistance to high-dose cytarabine [30••]. In another study by Eskelund et al. [31••] showed that a deleterious effect of TP53 mutations could not be overcome by even the high-intensity Nordic regimen (Maxi CHOP (cyclophosphamide, doxorubicin, vincristine, prednisone) and high-dose cytarabine). This signified the need for alternative therapies such as ibrutinib, an irreversible inhibitor of Bruton tyrosine kinase which was reported to show an objective response rate (ORR) of 68%, PFS of 14 months, and a complete response (CR) of 21% in a phase II trial [32, 33••].

Recently, Mori et al. [34] also presented two cases with L-NN-MCL who had progressive disease and required treatment. One of the patients showed complex cytogenetics which resulted in the loss of function of TP53 through chromosome 17 rearrangement. This patient converted into an aggressive form 5 years after the initial presentation. The second patient was found to have missense mutations in TP53 and KMT2a (MLL) genes as well as a frameshift mutation in BCOR gene (BCL-6 interacting co-repressor). Both patients were treated with rituximab 375 mg/m^2 monthly along with ibrutinib 560 mg daily

for 6 and 5 cycles, respectively. Normalization of white blood cell count, absolute lymphocyte count, and hemoglobin and platelets was achieved in 2 months, and complete remission was achieved before the ASCT. Both the patients are now to be disease free at > 24-months post-transplantation [34]. In our evaluation of the literature, we could not specifically identify the outcomes of patients with aggressive L-NN-MCL to targeted therapies such as ibrutinib.

ASCT has been shown to be beneficial on both PFS and OS in younger patients with MCL by the German Low-Grade Lymphoma Study Group as well as the European Mantle Cell Lymphoma Network [35–37]. The effect of ASCT on L-NN-MCL has been difficult to establish due to the low number of patients. In some cases, on non-nodal leukemic mantle cell lymphoma, especially the patients that present with splenomegaly, splenectomy has been shown to control the disease for some amount of time [14•, 17•, 38].

Summary and future directions

In conclusion, leukemic non-nodal MCL is an uncommon indolent form of MCL. It presents with isolated lymphocytosis and most patients are asymptomatic and do not have organ dysfunctions. Majority of these patients can undergo a "wait and watch" approach to prevent over-treatment. Genetic profiling, especially derangements in TP53 gene, may identify patients with a more aggressive disease. SOX11 negativity and hypermutated IGHV are important consideration in the recognition of indolent MCL. Aggressive leukemic non-nodal forms respond poorly to standard chemotherapy and a need for targeted agents in addition to immunotherapy may be more advantageous.

Compliance with Ethical Standards

Conflict of Interest
Akriti Gupta Jain, Chung-Che Chang, Sarfraz Ahmad, and Shahram Mori declare they have no conflict of interest.

Human and Animal Rights and Informed Consent
This article does not contain any studies with human or animal subjects performed by any of the authors.

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