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Risk Factors for Etiology and Prognosis of Mantle Cell Lymphoma

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Abstract

Non-Hodgkin lymphomas (NHLs) include any kind of lymphoma except Hodgkin's lymphoma. Mantle cell lymphoma (MCL) is a B-cell NHL and accounts for about 6% of all NHL cases. Its epidemiologic and clinical features, as well as biomarkers, can differ from those of other NHL subtypes. This article first provides a very brief description of MCL's epidemiology and clinical features. For etiology and prognosis separately, we review clinical, environmental, and molecular risk factors that have been suggested in the literature. Among a large number of potential risk factors, only a few have been independently validated, and their clinical utilization has been limited. More data need to be accumulated and effectively analyzed before clinically useful risk factors can be identified and used for prevention, diagnosis, prediction of prognosis path, and treatment selection.

Keywords

Mantle cell lymphoma; Risk factors; Etiology; Prognosis

1. Epidemiology, clinical features, and biomarkers

NHL is the seventh most common type of cancer in men and women in the U.S. There are over 30 subtypes of NHL, and different subtypes can differ in clinical and molecular features [1]. MCL is a rare subtype of NHL and comprises about 6% of all NHL cases. The goal of this study is to review risk factors of MCL identified in published studies. We first very briefly introduce its epidemiology, clinical features, and biomarkers. For more detailed discussions, we refer to recent reviews [2,3].

To a large extent, MCL is pathologically characterized by the detection of CD20, CD5, and CCND1 (cyclin D1). Its current definition was formulated in 1992. Its incidence rate is about 0.51 to 0.55 per 100,000 persons. In the U.S., there are currently about 15,000 MCL patients. These patients are typically Caucasian (about 2:1), male (about 2.5:1), and elderly

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(median age of diagnosis=68 years) [4]. MCL patients are usually present with extensive diseases, such as widespread lymphadenopathy, bone marrow involvement, splenomegaly, circulating tumor cells, and bowel infiltration [1]. U.S. cancer registry data shows an increase in the incidence of MCL between 1992 and 2007 [5]. This pattern is similar to that for NHL overall, whose age-adjusted incidence rate has increased from 11.07/100,000 in 1975 to 20.20/100,000 in 2008 [6].

The symptoms of MCL share certain similarities with those of other NHL subtypes. Enlarged lymph nodes are usually present, causing swellings on the neck, armpits, or groin. Multiple groups of lymph nodes are usually affected, and other body parts may also be affected as well. Bone marrow, liver, and GI tract involvement may occur. Other symptoms include loss of appetite and fatigue. About half of MCL patients experience fevers, night sweats, and weight loss known as “B symptoms”. Diarrhea and nausea may occur if the disease affects the bowel or stomach.

Diagnosis of MCL often requires removing an enlarged lymph node (a biopsy) and examining the cells under a microscope. Biopsies may also be taken from other body tissues. Other diagnosis methods, including cytogenetics and FISH (fluorescence in situ hybridization), are also used. PCR (polymerase chain reaction) and CER3 clonotypic primers are less commonly used [7]. Diagnostic techniques that have also been employed include blood tests, CT scans, X-rays, lumbar punctures, and bone marrow samples. These diagnostic tests may also assist in staging and predicting prognosis.

According to the Ann Arbor Classification, MCL has four stages. In Stage 1, only one group of lymph nodes is affected. In Stage 2, two or more groups are affected, and all of the affected lymph nodes are on the same side of the diaphragm. In Stage 3, the lymphoma is present in lymph nodes on both sides of the diaphragm. And in Stage 4, the lymphoma has spread beyond the lymph nodes to other areas such as bones, the liver, or the lungs. MCL patients are usually diagnosed at late stages (3 or 4). Beyond stage diagnosis, doctors also usually indicate whether B symptoms are present. Examined under a microscope, MCL cells typically look like those of a small cell lymphoma. However, clinically, MCL mostly behaves more like an aggressive lymphoma, with short responses to treatment and frequent relapses, and few patients can be cured with current therapies.

Most of the existing studies “embed” the investigation of MCL in that of NHL overall. Different from many published studies, this article is focused on MCL. The main goal is to provide an updated review of the risk factors that may be associated with the etiology and prognosis of MCL. The development and progression of MCL is extremely complex. To be comprehensive, this article covers clinical risk factors, environmental exposures, and molecular risk factors. We adopt a loose definition for “risk factors”. Factors included in the review are those that directly contribute to the development and progression of MCL, as well as those that may be involved in the pathogenesis and hence contribute to MCL in a less direct manner. Because of our limited knowledge, important risk factors and references will inevitably be missed. In addition, with the fast development in molecular profiling, this review may need to be updated in the near future.

2. Etiology

The development of MCL can be caused by multiple factors and their interplays [2,8]. For presentational clarity, below we review each type of risk factors separately.

2.1 Lifestyle and occupational risk factors

Several lifestyle factors have been suggested as associated with an increased risk of NHL overall and multiple subtypes in the pooled analysis of case-control studies within the International Lymphoma Epidemiology (InterLymph) Consortium (epi.grants.cancer.gov/InterLymph), which includes between 150 and 400 MCL cases and a large number of controls. Body mass index, cigarette smoking, and alcohol intake have been suggested as associated with NHL overall and some other subtypes [8] but not implicated as risk factors for MCL. Beyond differences between different subtypes, another possible reason for the lack of significant association for MCL is the relatively small number of cases [9,10,11], despite the fact that InterLymph is one of the largest studies on NHL. Additionally, recreational exposure to ultraviolet radiation has been associated with a reduced risk of NHL overall in some studies but not others. A similar reduction has been observed for MCL, although it is only borderline significant ($p\text{-value}=0.08$) [12]. Atopic disease has been suggested as associated with a reduced risk of NHL overall. However, an analysis has not been conducted separately for MCL [13]. Occupational exposure to pesticides and solvents has been implicated in the pathogenesis of B-cell lymphoma, and the amount of evidence has been increasing [14,15]. In a large, pooled, case-control study conducted in Europe, exposure to several solvents, including benzene, toluene, and xylene, was found to increase the risk of FL and CLL [16]. The risk of MCL was not assessed in that study. In the literature, the evidence has been conflicting. For example, in a recent meta-analysis, occupational exposure to gasoline, including benzene and a large number of other chemicals, was found to be not associated with the risk of NHL overall. Associations with individual subtypes were not evaluated [17].

2.2 Immune competence and infectious agents

Immune suppression has been connected to the risk of developing aggressive lymphomas [18]. Evidence has been accumulating from studies that involve medications suppressing the immune system. However, in a recent review, Smedby and Hjalgrim [2] suggested that there was no evidence of an increased risk of MCL in severely immunosuppressed individuals.

Multiple viruses have been implicated in the development of NHL overall [18]. Examples include EBV (Epstein-Barr virus), T-cell leukemia/lymphoma virus 1, hepatitis C virus, HHV-8 (human herpesvirus-8), HBV (hepatitis B virus), and others. However, according to an InterLymph study [19], there is still a lack of solid evidence for the association between these viral agents and the risk of MCL. On the other hand, there is increasing evidence for the role of antigenic drive, by exogenous or endogenous antigens, in the etiology of at least a subset of MCL cases [20]. Munksgaard and others [21] linked the risk of MCL with infection with European strains of the spirochete *Borrelia burgdorferi*, in particular when manifesting as a chronic inflammation of the skin known as Acrodermatitis atrophicans. In a large population-based Scandinavian case-control study, the self-reported history of *Borrelia*

and serologic evidence of past *Borrelia* infection were each associated with a 2 to 3-fold increased risk of MCL but not other NHL subtypes [22]. The association with MCL remained among patients who did not recall *Borrelia* infection but were tested positive for anti-*Borrelia* antibodies [21]. However, independent studies have not been able to confirm this association. For example, in an U.S. study, infection with strains of *B. burgdorferi* was not associated with an increased risk of MCL [23]. Frequent involvement of the gastrointestinal tract has been observed in MCL patients, leading to speculation that the risk of MCL development is associated with infectious agents that affect the gastrointestinal tract or cause a variation in microbial gut flora [24,25].

2.3 Family history

A family history of hematopoietic malignancies has been linked with a 2-fold increased risk of MCL [26], a magnitude similar to that for several other NHL subtypes such as DLBCL and FL but lower than that for CLL. This pooled study was based on self-reports of familial malignancies among MCL cases and controls [26]. The reliability of such data and results is subject to closer examination. Multiple factors may contribute to the observed familial aggregation, including for example the presence of inherited genetic susceptibility and the shared environmental exposures among family members. Tort and others [27] studied the DNA damage response genes and suggested that they could not account for the aggregation. Other genes and environmental exposures need to be more carefully measured and analyzed to determine the cause of familial aggregation.

2.4 Molecular risk factors

Multiple types of molecular measurements have been implicated in cancer development. Protein expression levels and functions may have the most direct associations with cancer outcomes and phenotypes. They are mostly regulated by mRNA sequences and expressions. Molecular features at the DNA/epigenetics level (e.g., copy number variation, methylation, and mutation status) affect clinical outcomes by influencing mRNA expressions. Similarly, microRNAs influence mRNA through translational repression or target degradation, which then affects clinical outcomes. Different types of molecular features do not function independently. However, as it is still an ongoing effort to study their interplays, and as the existing studies have been mostly focused on a single type of measurement, below we review different types of molecular factors separately.

The genetic hallmark of MCL is the t(11;14)(q13;q32) translocation, which leads to the overexpression of CCND1 [28]. Gene CCND1 can deregulate cell cycle control by overcoming the suppressor effect of retinoblastoma 1 (RB1) and the cell cycle inhibitor p27. Demonstration of CCND1 over-expression by immunohistochemistry or the t(11;14)(q13;q32) by molecular or cytogenetic methods has been critical in making a definitive diagnosis of most MCL cases. Although the t(11;14)(q13;q32) translocation occurs in the majority of MCL cases, there have been reports of a small subset of tumors that do not overexpress CCND1 or in which the t(11;14)(q13;q32) is absent [29,30,31]. Some studies have suggested that these CCND1-negative patients had poor clinical outcomes [32], while others [29] reported no difference in survival rates between CCND1-positive and CCND1-negative patients. The conflicting results can be partly explained by the insufficient

statistical power and the fact that some CCND1-negative MCLs are indolent. The CCND1-negative patients may demonstrate a gene expression signature and secondary molecular profile highly similar to the prototypical CCND1-positive MCL, which stresses the relevance of cell cycle dysregulation to the pathogenesis of MCL [33]. In CCND1-negative patients, translocations targeting CCND2 and CCND3 and their high expressions have been observed [30]. The proteins encoded by the cyclin family play important roles in cell cycle. They also have other functions for example being involved in the phosphorylation of tumor suppressor protein RB. In addition, MYCN, the amplification and overexpression of which can lead to tumorigenesis, has been suggested as a new oncogene for such patients [30].

In addition to the t(11;14)(q13;q32) translocation, MCL tumor cells may carry a large number of secondary chromosomal and molecular alterations targeting proteins that regulate the cell cycle and senescence (BMI1, INK4a, ARF, CDK4, and RB1) and interfere with the cellular response to DNA damage (ATM, CHK2, and P53). Using RNA sequencing techniques, Kridel and others [34] identified recurrent mutations in NOTCH1, which plays a role in a variety of developmental processes by controlling cell fate and decisions. Meissner and others [35] conducted a targeted sequencing of 18 genes (which were suggested in previous studies) and found frequent mutations in gene ATM, CCND1, TP53, NOTCH1, MEF2B, TRAF2, and TET2. The researchers stressed the identification of gene UBR5, which encodes a progesterin-induced protein belonging to the HECT family. This gene may have a role in the regulation of cell proliferation or differentiation. Biallelic deletions of region 9p21, which harbors gene p16INK4a and p14ARF, have been detected in about 20% of MCLs, often in those with an aggressive histology such as the blastoid variant [36]. Setoodeh and others [37] reported 4 cases of MCL with MYC translocation or MYC gene amplification. The protein encoded by gene MYC plays a role in cell cycle progression, apoptosis, and cellular transformation. MCLs with both CCND1 and MYC translocations are known as “double hit” lymphomas and can be aggressive and show a high proliferation rate due to the growth advantages. They can be distinguished from DLBCLs that have CCND1 and MYC translocations using SOX11 [38]. Schilling and others [39] performed M-FISH (multicolor FISH) analyses on 8 MCL cell lines and 9 MCL patients and identified recurrent breakpoints in 4p14, 5p15, 9q34, 10p11, 12q13, 13p11, 14p11, and 15q15. Flow-FISH and quantitative RT-PCR (real-time PCR) suggest TERT and CLPTM1L, both of which are important in apoptosis, as the target genes of 5p15.33 rearrangements. Salaverria and others [40] analyzed 22 MCL cases and 10 cell lines and found rearrangements in chromosomes 1, 8, and 10 in the tumors and 1, 8, and 9 in the cell lines. Kawamata and others [41] applied SNP-chip techniques and examined 33 samples of MCL (28 primary MCLs and 5 cell lines). Their study confirmed the known alterations, including the deletion of INK4A/ARF, the duplication/amplification of MYC, the deletion of ATM, and the deletion of TP53. In addition, the researchers also identified a duplication/amplification that occurred at 13q involving oncogenic microRNA miR17-92. Other notable findings included the duplication/amplification of CCND1, del(1p), del(6q), dup(3q), and dup(18q) and a number of aUPD (acquired uniparental disomy) sites including whole chromosome 9 aUPD and 9p aUPD. Similar findings were made in a study with 10 cell lines and 28 primary tumors [42]. Menanteau and Martinez-Climent [43] provided comprehensive discussions of genomic aberrations in MCL. They demonstrated that the introduction of higher resolution

techniques has led to the identification of many putative target genes, especially in the area of homozygous loss. Notable recent findings include the bi-allelic deletion of chromosomes 1p33 involving FAF1 and CDKN2C genes; 2q13 targeting BCL2L11, which belongs to the BCL-2 family and may function as an essential initiator of apoptosis; 2q37 (associated with the down-regulation of the SP100 gene); and 19p13.3 including the TNF superfamily genes 7, 9, and 14, which are involved in apoptosis. Based on an integrative analysis of high-resolution RNA expression and genomic microarray data, Hartmann and others [44] identified genes with down-regulated expressions in MCL patients in areas of heterozygous loss, including PROX1 (1p32), MCPH1 (8p21.3), ING1, and CUL4A (13q34). These results may suggest that the deregulation of the Hippo signaling pathway, which controls organ size through the regulation of cell proliferation and apoptosis, may have a pathogenetic role in MCL because several members (MOBK2A, MOBK2B, and LATS2) showed decreased expressions in MCL cells. Similarly, a different study reported decreased expressions of the genes encoding the TRAIL receptors DR4 and DR5, which are involved in apoptosis, in MCL cells with deletion of chromosome 8p21 [45]. One study identified monoallelic deletion of the RB1 gene (a major tumor suppressor) at 13q14.2 with the presence of inactivating mutations in the remaining allele in MCL cells [46]. More frequently, homo- and hemi-zygous deletion of the TNFAIP3 gene (which inhibits NF-kappa B activation as well as TBF-mediated apoptosis) at 6q23.3, in combination with inactivating mutations or promoter hypermethylation, has been found in MCL and other B-cell lymphomas [47]. Several putative oncogenes targeted by high-level chromosomal amplification in MCL cells have been identified, including MAP6 in 11q13, CENTG1 in 12q14, and the miR-17-92 cluster in 13q31. However, only a few of those genes (for example, TNFAIP3, CDKN2C, BCL2L11, and miR-17-92) have been functionally validated, and most others need further examinations.

Beyond CCND1, another gene that may have an important role in MCL etiology is the neural transcription factor SOX11 [48,49], although its involvement is still being debated. SOX11 is involved in the regulation of embryonic development and determination of cell fate. It is overexpressed in most MCLs but is not detected in other mature B-cell lymphomas or normal lymphoid cells. There are also SOX11-negative MCLs. In a functional study, Vegliante and others [50] showed that SOX11 promoted tumor growth in a mouse model and suggested that SOX11 contributes to tumor development by altering the terminal B-cell differentiation program of MCL. A recent study [30] suggested that SOX11 can be a good marker to identify CCND1-negative patients with poor outcomes. Hamborg and others [51] developed an RT-qPCR assay and demonstrated the potential clinical value of SOX11. SOX11, SOX4, and SOX12, which all belong to the SOXC family, compete for the same target genes. Wasik and others [52] reported the variable expression of SOX4 and high expression of SOX12 in MCLs compared to normal tissues and showed that the expression of SOXC genes is highly correlated in SOX11-positive MCL.

Down- or up-regulations of a few other genes may also contribute to the etiology of MCL. The proto-oncogene BMI1 is frequently up-regulated in MCL [53]. This gene regulates p16 and p19, which are cell cycle inhibitor genes. Gelebart and others [54] conducted a study with 4 MCL cell lines and 15 tumor samples and reported that FASN (fatty acid synthase), a

key player in the *de novo* synthetic pathway of long-chain fatty acids, was highly expressed in MCL. In contrast, benign lymphoid tissues and peripheral blood mononuclear cells from normal samples were negative.

Genetic association studies have been conducted and identified multiple potentially risk-associated SNPs. In a study recently conducted in northern Europe with 120 MCLs, TNF rs1800629 was associated with an increased risk of MCL (OR=2.8, 95% CI 1.4–5.9) [55]; however, this association was not confirmed in a large, pooled study [11]. IL10 rs1800890 was also associated with an increased MCL risk in the European study, whereas the pooled study reported that IL10 variant rs1800896 was risk-associated [56]. IL 10 is involved in B cell survival, proliferation, and antibody production. Functional studies have shown that the TNF rs1800629 minor allele is associated with elevated levels of the TNF-alpha protein, and IL10 rs1800890 indirectly affects TNF-alpha levels through decreased down-regulation of TNF. TNF is a key activator of inflammation through the NFkB (nuclear factor-kB) pathway and promotes cell proliferation, survival, invasion, and angiogenesis. The identification of TNF SNPs suggests that a proinflammatory milieu is involved in the pathogenesis of MCL. Genetic variants in the HLA region, which is essential for immune function and associated with multiple cancers and other NHL subtypes [18], have not been associated with the risk of MCL [57]. With 32 MCL patients and 58 controls, Galimberti and others [58] investigated SNPs in the VEGF (vascular endothelial growth factor) genes, which encode proteins stimulating vasculogenesis and angiogenesis. It was found that the VEGF G+405C and C-2578A SNP allele distribution was significantly lower in MCL than among normal controls (p-value=0.014, p-value=0.001).

Epigenetic factors have also been studied. A survey of the role of epigenetics in B-cell lymphomas was recently conducted [59]. In one of the first comprehensive descriptions of the MCL epigenetic landscape [60], it was found that MCLs had twice as many aberrantly hypomethylated as hypermethylated loci, the gene networks most heavily affected by aberrant DNA methylation revolved around NFkB (which plays a key role in regulating immune response to infection) and HDAC1 (which, together with metastasis-associated protein 2, deacetylates p53 and modulates its effect on cell growth and apoptosis); and gene expression was inversely correlated with methylation at over 1400 loci. CD37 (which plays a role in the regulation of cell development, activation, growth, and motility) was found hypomethylated and overexpressed, whereas CDKN28, HOXD8, MLF1, and PCDH8 were hypermethylated and silenced. As discussed by Shaknovich and Melnick [59], there are a few other studies on the epigenetics of B-cell lymphoma overall, but the research on MCL remains limited.

Progress has been made in understanding the role of microRNAs in MCL. A comprehensive review was recently conducted [61]. Comparing MCL tumor samples with their normal counterparts has led to the identification of differentially expressed microRNAs with roles in cellular growth and survival, and microRNA expression profiles have been linked with differences in clinicobiological characteristics. The deep sequencing of the small RNA transcriptome of normal and malignant B-cell samples including MCLs has led to the identification of over 300 risk-associated microRNAs [62]. Jardin and Figeac [63] argued that almost all mature lymphoid malignancies can be characterized by distinct microRNA

profiles. Further, miR-155 and miR-17-92 have been suggested as crucial in the pathogenesis of MCL. miR-155 may inhibit malignant growth and viral infections. The miR-17 family miRNAs have been implicated in a wide variety of malignancies and are referred to as oncomirs.

More recently, experiments have also focused on searching for proteomic markers. Cecconi and others [64] used MCL cell lines and identified several proteins, including for example NFkB and the phosphoinositide-3 kinase-mammalian target of rapamycin (PI3K-mTOR), which can be linked to a specific signal transduction pathway and can be important players in MCL pathogenesis. Their study also identified the mitochondrial signaling pathway (which is heavily involved in apoptosis) that has MAPK1, CK2, CK1, PKCzeta, and PKCepsilon as candidate upstream molecules.

3. Prognosis

The overall 5-year survival rate for MCL is about 50% (for advanced-stage MCL) to 70% (for limited-stage MCL). In comparison, for NHL overall and DLBCL, the 5-year survival rates are about 63% and 58%, respectively. Many MCL patients are diagnosed at advanced stages. Most of the indolent MCLs are diagnosed at stage 4, due to the high levels of lymphocytosis. As a result, prognosis has been problematic, and indexes usually do not work well. Staging can be used but is not very informative. As malignant B-cells can pass freely through the lymphatic system, the concept of metastasis does not really apply.

3.1 MIPI

For NHL overall, the International NHL Prognostic Factors Project developed a predictive model in 1993 that included 5 factors: age, tumor stage, serum concentration of LDH (lactate dehydrogenase), performance status, and number of sites of extranodal disease. This prediction index has been referred to as the IPI (International Prognostic Index) and validated in multiple independent studies.

For front-line MCL, MIPI (the MCL International Prognostic Index) has been developed using data on 455 advanced-stage patients treated within randomized trials of the European MCL Network [65]. Among the evaluable patients, approximately 18% were treated with high-dose therapy and stem cell transplantation in the first remission. In univariate analysis, factors identified as associated with shorter overall survival included higher age, worse ECOG (Eastern Cooperative Oncology Group) performance status, presence of B-symptoms, spleen involvement, larger tumor size, higher WBC (white blood cell) counts, higher lymphocyte, granulocyte, and monocyte counts, higher LDH, lower hemoglobin, and higher beta-2-microglobulin levels. In contrast, patient sex, Ann Arbor stage (III versus IV), bone marrow involvement, number of involved nodal areas, number of involved extranodal sites, platelet count, and albumin level, which had been indicated in the survival rates of other subtypes, were not prognostic for MCL. Using multivariate analysis, the MIPI prognostic score is defined as a continuous variable for which a higher value is associated with shorter overall survival. More precisely, it is equal to

$$0.03535 * age (years) + 0.6978 (if ECOG > 1) + 1.367 * \log_{10}(LDH / ULN) + 0.9393 * \log_{10}(WBCs \text{ per } 10^{-6} L).$$

In the above formula, ULN denotes the upper limit of normal, which is known to vary across studies. MIPI is able to classify patients into 3 risk groups: low risk (median survival not reached after median 32 months follow-up and 5-year OS rate of 60%), intermediate risk (median survival of 51 months), and high risk (median survival of 29 months). In addition to the 4 independent prognostic factors included in the model, the cell proliferation index Ki-67 has also been shown to have additional prognostic relevance. (More details are provided below.) When the Ki-67 measurement is available, a biologic MIPI can be calculated. MIPI has been externally validated by several independent studies. For a comprehensive review and discussion, we refer to [66]. MIPI may not be applicable to progression-free survival, which depends more on specific treatment regimens.

3.2 Other prognostic factors

Beyond those included in MIPI, a few other prognostic factors have been suggested. Ki-67 is a protein encoded by gene MTK167 and may be necessary for cellular proliferation. It is an indicator of how fast cells mature and is expressed in a range of about 10%–90%. The lower the percentage, the lower the speed of maturity, and the more indolent the disease. Katzenberger and others [67] analyzed survival for subgroups of patients with varying Ki-67 indices. It is shown that the median survival time was about 1 year for 61–90% Ki-67 and nearly 4 years for a 5–20% Ki-67 index.

MCL has 3 histologic variants: diffuse, nodular, and mantle zone. Diffuse and nodular MCLs have a poor overall survival rate (and possibly a poor response to treatment) [68], and the mantle zone variant exhibits the attributes of a low-grade lymphoma. MCL has 2 main cytologic variants: typical and blastoid. Typical cases are small to intermediate-size cells with irregular nuclei. Blastoid variants have intermediate to large-size cells with finely dispersed chromatin. A blastoid is faster-growing, and it is harder to get long remissions. Survival of most blastoid variants is shorter, although a subset may survive for up to 5 years [69].

Beta-2 microglobulin, which is necessary for the cell surface expression of MHC class I and the stability of the peptide binding groove, is another potential risk factor in MCL prognosis used primarily for transplant patients. Khouri and others [70] studied MCL patients with stem-cell transplantation (SCT). It was shown that values of beta-2 microglobulin less than 3 yielded 95% overall survival up to 6 years, whereas over 3 yielded a median overall survival of 44 months.

3.3 Molecular risk factors

SOX11 has been suggested in some studies as carrying prognostic information, but the results have been conflicting. Wang and others [71] reported that, in MCL with lymph node presentation, the absence of nuclear SOX11 was associated with a shorter overall survival. In contrast, another study reported that a subset of SOX11-negative MCL, carrying the t(11;14) translocation but with a non-nodal, leukemia presentation, has an indolent clinical

outcome [72]. In a population-based cohort of 186 MCL patients, Nygren and others [73] found that SOX11-negative patients had a shorter overall survival. However, in multivariate analysis, SOX11 was no longer significant. Navarro and others [74] conducted an integrative and multidisciplinary analysis of data on 177 MCL patients. It was found that nodal presentation and SOX11 expression were predictive for poor overall survival. In multivariate analysis, IGHV gene status and SOX11 expression were identified as independent risk factors for prognosis. In B-cell neoplasms in general, mutations of IGHV have been associated with better responses to some treatments and with prolonged survival.

Molavi and others [75] correlated the expression of SOCS3 and overall survival by analyzing 33 randomly chosen MCL patients. SOCS3 is a negative regulator of signaling pathways including those of STAT3 and NFkB. It was found that in 19 patients aged lower than or equal to 69 years at the time of diagnosis, those that carried SOCS3-negative tumors showed a trend toward a borderline significantly worse outcome (p-value=0.1). With 92 MCL patients (among whom 64 died during followup), Rosenwald and others [76] profiled 8810 mRNA gene expressions and identified 20 proliferative genes, including CDC2, ASPM, tubulin- α , and others. Among them, CDC2 is a key player in cell cycle regulation, and gene ASPM is essential for normal mitotic spindle function. Recent studies have also suggested the role of the B-cell receptor (BCR) signaling pathway in MCL survival [77]. BCR is a key survival molecule for normal B cells. Defects in BCR signal transduction may lead to immunodeficiency, auto-immunity, and B-cell malignancy. This pathway has also been shown to have important implications in therapeutic development.

Using CGH analysis, Bea and others [78] reported that the number of chromosomal gains, losses, and DNA amplifications was significantly higher in the blastoid variants, particularly the gains of chromosomes 3q and 12q and losses of 9p and 17p. The gains or amplification of chromosomes 3q27-q29 and 12q14-q15 (which invoke the CDK4 and MDM2 genes and are involved in the phosphorylation of oncogene RB) have been associated with shorter survival [79]. In addition, a number of chromosomal losses such as 9p21 (targeting CDKN2A which functions as a stabilizer of P53), 17p13 (P53), 8p21, 13q14 (miR-15a/miR-16), and 9q21-q22 have been associated with poor prognosis in different studies [80]. The gain of chromosome 8q involving the MYC gene locus has been detected in MCL with a very rapid clinical progression. Accordingly, MYC rearrangements, either at diagnosis or at relapse, may serve as a negative prognostic factor [81]. Deletions or mutations in the ATM locus occur both in classical and blastoid variants and are not related to prognosis [80,82], suggesting that this alteration is in early lymphomagenesis. For several common genomic abnormalities that are correlated with poor prognosis, such as the amplification of 3q27-q29 and the deletions of 8p21 and 9q21-q22, the target genes have not been identified. Several of the above genetic alterations have been confirmed in SNP-array and CGH-array studies. For a recent review, we refer to [83].

In epigenetic research, Enjuanes and others [84] identified 5 genes (SOX9, HOXA9, AHR, NR2F2, and ROBO1) frequently methylated in MCL tumors. The observed methylations were more likely to occur in the same primary tumors. They were associated with a higher proliferation rate and an increased number of chromosomal abnormalities, as well as poorer prognosis. Molavi and others [75] found that SOCS3 was consistently methylated in

SOCS3-negative cell lines (3/4) and tumors (7/7) but was not methylated in 1 SOCS3-positive cell line and 5 SOCS3-positive tumors.

Iqbal and others [85] conducted genome-wide microRNA profiling on 30 CCND1-positive MCL patients, 7 CCND1-negative patients, and others. A 19-microRNA classifier was identified, which included 6 up-regulated and 13 down-regulated microRNAs. This classifier could distinguish MCL from other aggressive lymphomas. In addition, microRNAs were also found to be associated with prognosis. The poor prognosis group was characterized by high expressions of miR-18a of the miR17-92 cluster and miR-18b, miR-20b, and miR-363 of the miR-106a-363 cluster. The miR-106a cluster also belongs to the miR-17 precursor family, whose functions have been briefly mentioned above. The good prognosis group was characterized with higher expressions of miR-125-3p, miR-126, miR-10b, miR-143, and miR-145. In a recent study [86], miR-127-3p and miR-615-3p were found to be significantly associated with MCL overall survival. Also, miR-127-3p was combined with Ki-67 to create a new prognostic model. A similar model was created with miR-615-3p and MIPI. Navarro and others [87] found 7 microRNAs with prognostic significance independent of IGHV status and SOX11 expression.

Minimal residual disease (MRD) has been implicated in the prognosis of other subtypes of NHL. It may also affect MCL prognosis and be a cause of relapse. Results from the European MCL network have suggested that MRD assessment can be suitable for investigating the potential of new treatment modalities, as well as the efficiency of new drugs [88].

4. Expert commentary

As a rare subtype of NHL, MCL has many of the clinical and molecular features different from other subtypes. A few epidemiologic studies have been conducted [2]. In the U.S., incidence and prognosis statistics have been generated using SEER (Surveillance Epidemiology and End Results) and other cancer registry data. Research on the risk factors for the etiology and prognosis of MCL has been limited and quite often “embedded” in that on NHL overall. Such risk factors may have important practical implications. Specifically, they can be used to report and compare risk profiles of patient groups, to stratify randomization in clinical trials, to perform risk adjustment in epidemiological studies, and to conduct risk-adapted treatment strategies.

For presentational clarity, we have provided separate discussions on clinical risk factors, environmental exposures, and molecular risk factors. The development and progression of MCL is a complex process, involving the joint effects of multiple families of risk factors and their interactions. A few observational studies and clinical trials have been conducted on clinical risk factors and environmental exposures. Compared to NHL overall and larger subtypes, fewer risk factors have been identified, and some results in published studies have been conflicting. Multiple factors may have contributed to such results. Because of MCL’s low incidence rate, the existing studies usually have small to moderate sample sizes, making them not sufficiently powered. MCL epidemiologic studies face similar challenges as other cancers. For example, studies conducted in different populations can be confounded by

genetic heterogeneity. The analysis of family history data may be confounded by a large number of factors. The quality of self-reported data is subject to closer examination. Certain data collection techniques (for example, serologic testing in the study of *Borrelia*) have limitations. In addition, different studies usually collect different sets of measurements. Adjusting for different sets of confounders could also result in different conclusions on the significance of risk factors. As these challenges are shared by other cancer studies, we choose not to provide detailed discussions here.

Profiling studies have searched for genetic, genomic, epigenetic, and proteomic risk factors. The genetic hallmark of MCL is *CCND1*, although there are also a small number of *CCND1*-negative MCLs. Other notable findings include *SOX11*, *NOTCH1*, *ATM*, and others. From a biological point of view, there are credible interpretations of their involvements in MCL pathogenesis. For example, they are related to the hallmarks of cancer such as apoptosis, cell cycle, and DNA repair. However, as discussed above, there are conflicting results on the associations between these genes and clinical outcomes. A representative example is the controversy regarding *SOX11*. High-throughput profiling studies share similar challenges as “classic” epidemiologic studies and clinical trials. In addition, they face unique problems, as discussed in great detail by Rebbeck and others [89]. For example, with genomic data, it is commonly agreed that there are very few “mountains” while a lot of “hills”. The lack of strong signals, coupled with the small sample sizes, may contribute to the conflicting observations. Many of the existing molecular studies have targeted identifying individual genes, SNPs, methylation loci, etc. Genetic and epigenetic units (for example, multiple SNPs within the same genes) may function in a concordant manner. There are a few studies taking more of a system biology perspective and attempting to draw conclusions at a hierarchically higher level. An example is the study on the BCR signaling pathway. We observe that most of the findings are on “classic” cancer pathways (for example, those related to cell cycle, apoptosis, DNA repair, and signaling). Such results are “as expected” and reasonable. On the other hand, these pathways are involved in a large number of cancer types and are unlikely to be able to define the unique characteristics of MCL. More MCL-specific genes and pathways remain to be identified. With a few exceptions, we have mostly focused on qualitative results. For MCL, there is still a lack of consensus on the set of risk factors and “directions” of their effects (positively or negatively associated with the outcome). Thus, discussing the detailed quantitative results may not be very sensible.

Statistics plays an important role in the analysis of complex profiling data [8]. Many of the existing MCL molecular studies are still confined to “classic” single-marker analysis. There are only a handful of studies conducting the joint analysis of a large number of (epi)genetic markers, pathway analysis, or accounting for gene-environment/gene-gene interactions. More effectively analyzing the existing data using more advanced statistical methods may also solve some observed conflicts and lead to new findings.

There are very few factors that have been established as directly contributing to the risk and progression of MCL. Thus, as stated in the first section, we take a very loose definition of “risk factors”. Those reviewed in this article may directly contribute to the development and progression of MCL. It is also possible that they are involved in pathogenesis and contribute

in a less direct manner or are even simply correlated with truly causal risk factors. Our literature review suggests that most of the existing studies have focused on identifying factors associated with risk or prognosis. There is a lack of research discriminating “passengers” from “drivers”. Identifying the associated factors can be the very first step. Functional experiments need to be carefully designed and conducted to identify causal risk factors and build comprehensive indexes. Because of our limited knowledge and the limited scope of this article, it is inevitable that many important results are not reviewed and relevant references not cited.

An important goal of identifying risk factors is to design effective treatment regimens. In this article, we have mostly focused on the lists of risk factors and their biological mechanisms. The clinical applications have been largely neglected. In a few recent studies [90,91,92,93,94], it has been demonstrated that molecular markers can assist therapeutic development.

Five-year view

A major limitation of the existing studies is the insufficient power. In addition, different studies may have samples with incomparable characteristics. For example, the genetic heterogeneity in InterLymph may be higher than that found in the European MCL network study. To unify findings in the literature, it is important to revisit existing data, carefully compare sample characteristics across studies, reanalyze data, and conduct subset-analysis or marching to obtain more comparable samples. The fast development of profiling techniques has led to promising findings. We expect more breakthroughs in the identification of molecular risk factors, especially with the increasing utilization of deep sequencing techniques. As described above, such sequencing has led to interesting findings on susceptibility microRNAs. However, in general, their applications in MCL are still limited. Many of the existing studies have taken a candidate gene approach, while we expect to see more whole-genome studies in the next couple of years. Another limitation of the existing molecular studies is that they are often “one-dimensional” and focused on a single type of molecular measurement. Multiple genetic and epigenetic changes simultaneously contribute to cancer development, and a single type of molecular measurement cannot provide a comprehensive description of the cancer process. TCGA (The Cancer Genome Atlas) and ICGC (the International Cancer Genome Consortium) have been conducting comprehensive profiling on multiple cancers including NHL. We expect a similar effort specifically for MCL, too. With such data, there is a possibility of clarifying some of the existing controversies and building multidimensional (epi)genetic profiles. Most of the risk factors reviewed in this article (and identified in many published studies) are associated with etiology and prognosis “on average”. That is, they are population-level results. There are some studies trying to more precisely characterize subsets of MCLs. We expect to see more of such results with the collection of sequencing data. With accumulating studies on the molecular risk factors, we also expect to see more of their clinical applications.

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* of interest

** of considerable interest

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Key issues

- MCL is a rare, mostly aggressive subtype of NHL. Because of its low incidence rate, research on MCL remains limited.
- The epidemiology, etiology, and prognosis patterns of MCL may differ from those of the other NHL subtypes.
- For etiology, a few lifestyle and occupational risk factors have been suggested, although not all have been confirmed. There is also evidence highlighting infectious agents and family history.
- In molecular studies, the most notable finding is CCND1. Other findings include SOX11, NOTCH1, ATM, and others. There are conflicting observations in the literature. Additionally, microRNA, methylation, and proteomic risk factors have also been suggested.
- For prognosis, the MIPI has been developed using age, ECOG performance status, LDH, and normalized WBC and has been validated in independent studies.
- Other possible prognostic factors include Ki-67, cell type, Beta-2 microglobulin, and others.
- A large number of molecular risk factors have been suggested, including SOX11, SOCS3, the BCR signaling pathway, and others. Epigenetic risk factors have also been suggested.
- There is a lack of consensus on risk factors. More carefully designed and controlled epidemiologic studies/clinical trials and more comprehensive profiling studies are needed.