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Recognizing nodal marginal zone lymphoma: recent advances and pitfalls. A systematic review

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ABSTRACT

The diagnosis of nodal marginal zone lymphoma is one of the remaining problem areas in hematopathology. Because no established positive markers exist for this lymphoma, it is frequently a diagnosis of exclusion, making distinction from other low-grade B-cell lymphomas difficult or even impossible. This systematic review summarizes and discusses the current knowledge on nodal marginal zone lymphoma, including clinical features, epidemiology and etiology, histology, and cytogenetic and molecular features. In particular, recent advances in diagnostics and pathogenesis are discussed. New immunohistochemical markers have become available that could be used as positive markers for nodal marginal zone lymphoma. These markers could be used to ensure more homogeneous study groups in future research. Also, recent gene expression studies and studies describing specific gene mutations have provided clues to the pathogenesis of nodal marginal zone lymphoma, suggesting deregulation of the nuclear factor kappa B pathway. Nevertheless, nodal marginal zone lymphoma remains an enigmatic entity, requiring further study to define its pathogenesis to allow an accurate diagnosis and tailored treatment. However, recent data indicate that it is not related to splenic or extranodal lymphoma, and that it is also not related to lymphoplasmacytic lymphoma. Thus, even though the diagnosis is not always easy, it is clearly a separate entity.

Introduction

The current World Health Organisation (WHO) classification for hematopoietic neoplasms enables the accurate diagnosis of most lymphoma types. Some problem areas, however, remain, one of which is the diagnosis of nodal marginal zone lymphoma (NMZL). The identification of NMZL has been difficult because of the rarity of this disease and the lack of positive immunohistochemical or molecular markers. As a result, epidemiology, prognosis, and therapeutic options have not been firmly established. In this review, we provide an overview of the current knowledge on NMZL with special emphasis on diagnostic criteria and pathogenesis, based on a systematic review of the literature.

We performed a PubMed search in October 2012 with the key words “NODAL MARGINAL ZONE LYMPHOMA”, “MONOCYTOID B-CELL LYMPHOMA”, “NODAL MZL”, and “NODAL MZLS”, and filtered for publications in the English language. After removal of duplicates, 167 hits were retrieved, including articles from 1986 until 2012. Only papers published after 1994 were included, coinciding with the adoption of the REAL classification, after which NMZL and extranodal MZL (EMZL) became more clearly separated in literature. From the remaining 116 articles, the abstracts of all articles were read by one of the authors (MvdB). Twenty-five papers were excluded because they dealt with EMZL or other entities, and four papers were excluded because NMZLs represented only a very minor part of a larger series (i.e. only 1 or 2 cases of NMZL, comprising less than 10% of cases). The remaining 87 papers were read in their entirety, and included if deemed relevant for this review. Additional papers were included from bibliographies.

Classification of NMZL

According to the current (2008) WHO classification, NMZL is “a primary nodal B-cell neoplasm that morphologically resembles lymph nodes involved by MZL of extranodal or splenic types, but without evidence of extranodal or splenic disease”. This means that for a diagnosis of NMZL, integration of clinical and pathological data is required. It also implies that NMZL is a diagnosis of exclusion. Also, this definition has resulted in putting the three categories together into one larger group, thus obscuring the important differences between them.

Marginal zone lymphomas were initially classified as ‘monocytoid B-cell lymphomas’. This term was put forward by Sheibani et al. in 1986 in a paper describing lymphomas consisting of cells that resemble the monocytoid B-cells observed in reactive conditions like lymphadenitis in toxoplasmosis and HIV lymphadenopathy. At that time, there was no strict separation between nodal and extranodal MZLs. The revised Kiel classification from 1990 introduced the separation between nodal and extranodal marginal zone lymphoma (EMZL). Shortly thereafter, multiple papers emphasized the morphological similarities between EMZL (at that time referred to as MALT lymphoma, i.e. lymphoma of the mucosa associated lymphoid tissue) and NMZL. In the REAL classification of 1994, and in the 2001 WHO classification, NMZL was adopted as a provisional entity. In the current 2008 WHO classification, NMZL has become a definitive entity and a pediatric variant has been included.

It has not been firmly established whether MZL of Waldeyers ring should be considered NMZL or EMZL. A recent Korean study suggests that, because of the overlap in prognosis, MZL of Waldeyers ring resembles NMZL rather than EMZL.
**Epidemiology and etiology**

NMZL is a rare lymphoma, accounting for 1.5-1.8% of lymphoid neoplasms.10 The incidence of NMZL appears to be increasing, which is most likely due to a ‘real’ increase, rather than better recognition.11 Most studies report a median age around 60 years with a wide age distribution ranging from adolescence to patients over 90 years old.2,20 Both sexes are affected with approximately equal frequency.

Morphologically, NMZL resembles EMZL. EMZL is well known for its association with conditions that provide a chronic stimulation to the immune system, including chronic infections (e.g. Helicobacter pylori infection in gastric EMZL) and autoimmune conditions (e.g. salivary gland EMZL in Sjögren’s syndrome). From this, one could hypothesize that NMZL, or a subset of NMZLs, might also be caused by specific chronic inflammatory conditions. Indeed, infections and autoimmune disorders have been reported in association with NMZL, but this evidence remains far from sufficient to establish a definitive role for these stimuli in lymphomagenesis. Recently, we encountered a case of what we had referred to as NMZL. This case implies that without extensive workup, including gastric biopsies, one cannot be sure that a case of NMZL really represents this entity.

Hepatitis C virus (HCV) has been reported in a subset of NMZL patients. In an early but small study, monocytes of B-cell lymphoma had the highest prevalence of HCV in comparison with other lymphoma types.21 In a larger study by Arcaini et al.,9 of 38 (24%) patients with NMZL had positive serology for HCV, in one patient combined with positive hepatitis B virus (HBV) serology.22 Some other studies confirmed an association with HCV in a smaller proportion of patients (Camacho et al. and Oh et al. in 20% and 5%, respectively),23,24 but other studies did not.25 The study by Camacho et al. also showed HBV infection in 50% of patients. The difference in HCV prevalence in NMZL between studies might be caused by geographical variation, which also appears to hold true for HCV prevalence in lymphoplasmacytic lymphoma, an entity closely related to NMZL.23-25

NMZL has also rarely been described in human immunodeficiency virus-infected patients, and complete regression of transformed NMZL has been reported in one such patient after anti-retroviral therapy.26

The composition and use of the different variable families on the immunoglobulin heavy chain locus have been connected to certain diseases in specific lymphoma types. In NMZL, multiple studies have shown biased use of immunoglobulin heavy chain VH families VH3 and VH4, in particular VH4-34.27-29,31,32 Preferential use of VH4-34 is associated with Epstein-Barr virus and cytomegalovirus in patients with chronic lymphocytic leukemia.27 In NMZL, an association with these viruses has not been established.33-36 In NMZL patients with HCV, VH1-69 was used preferentially, which is in line with other studies that describe the preferential use of VH1-69 in response to the E2 antigen of HCV.31,35

Many studies have reported autoimmune diseases in association with NMZL and include rheumatoid arthritis, vitiligo, systemic lupus erythematosus, autoimmune hemolytic anemia, chronic thyroiditis, and Sjögren’s syndrome.34-36 In these studies, 6-19% of patients had an autoimmune disease. To summarize, there are indications that NMZL is associated with chronic inflammation, but the precise mechanisms remain unknown.

**Clinical and laboratory features of patients with NMZL**

The clinical features at presentation are summarized in Table 1.2,9,15-19 Most patients with NMZL present with peripheral lymphadenopathy; a very small minority of patients have only central lymphadenopathy at presentation. The head and neck lymph nodes are most frequently involved. Bulky tumors (> 5 cm) are observed in 11-31% of patients. Across studies, roughly half the patients present with stage III or IV disease and 10-20% of patients experience B symptoms. Anemia is present with varying frequency (11-36%).9,14-16,20 If these studies are taken together, approximately one quarter of patients are anemic. Thrombocytopenia has been described in one study in one-tenth of patients.9-11 Involvement of the peripheral blood is reported in 10-24% of patients.9-10 The incidence of bone marrow involvement varies greatly between studies (from 0-62%), but an overall appraisal of the data shows that the bone marrow is involved in approximately one-third of patients.9,12,13-14,18-20

Positron emission tomography (PET) using (18)F-fluorodeoxyglucose appears to be a good way to study disease extent in NMZL, considering the PET-positivity in the large majority of cases reported so far (92% of 14 cases).9,41

Serum lactate dehydrogenase (LDH) is elevated in 12-48% of patients, beta 2 (b2)-microglobulin is increased in 29-45%,9,10,13,15-17 An M-component is present in 6-33% of patients.9,12-14 In one study, cryoglobulins were present in only 2 of 14 patients.15 Hypoalbuminemia was reported in 7-10% in two studies.9,17

To summarize, the clinical presentation of NMZL is non-specific and highly variable, but this may be due to the difficulty of the diagnosis and the variable rigor by which other entities have been excluded.

**Cell of origin**

Marginal zone lymphoma receives its name from the resemblance to the physiologic marginal zone. The marginal zone surrounds the mantle zone of the germinal center and is usually not recognized morphologically in lymph nodes. However, the spleen and some mesenteric lymph nodes do show a marginal zone in normal situations, and, occasionally, other lymph nodes also have marginal zone development.41

NMZL arises from mature B cells that have rearranged immunoglobulin genes, and can, therefore, be detected in clonality studies. However, the precise B-cell of origin of NMZL remains poorly defined and it has been suggested that NMZL can arise from different subsets of mature B cells, not necessarily being marginal zone B cells. Multiple small studies have examined the presence of somatic hypermutation (SHM), which was detected in the large majority of cases (in approximately 85%).13,15,18,28,41 suggesting a (post-)germinal center B cell. However, less than half the cases showed evidence of antigen selection. The study by Conconi and colleagues showed ongoing mutations in 4 of 6 hypermutated cases, suggesting derivation from germinal center B cells.41 Although the presence of SHM suggests post-germinal center derivation, there is accumulating evidence for germinal center-independent SHM. This evidence comes from patients with hyper-IgM syndrome.
and X-linked lymphoproliferative disorder, who lack functional germinal centers, but do show some SHM.\textsuperscript{43,44} Multiple other studies have also shown germinal center-independent SHM.\textsuperscript{45,46} Very recently, Warsame and associates showed evidence of ongoing mutations in microdissected monocytoid B cells.\textsuperscript{47} In addition, these cells expressed activation-induced cytidine deaminase, which is required for SHM.

The name NMZL suggests derivation from marginal zone cells, and the expression of MINDA and IRTA1 in many cases (see below) supports this notion; the data so far are, however, still conflicting.

**Histopathology**

NMZL has great variability in growth pattern and cellular morphology and is, therefore, almost never a ‘spot diagnosis’. Rather, a diagnosis of NMZL requires careful integration of morphology, immunohistochemistry, molecular studies, and clinical features (Figure 1).

On low power, multiple growth patterns can be recognized, as was nicely illustrated by Salama and colleagues.\textsuperscript{48} In their study, a diffuse pattern of infiltration was most frequent (in 51 of 51 cases), followed by interfollicular and nodular patterns of infiltration in 14% and 10%, respectively. Perifollicular growth was reported in only one case. In a study by Traverse-Glehen\textsuperscript{et al.} of 21 patients, nodular and interfollicular growth was most frequently observed, both in one-third of patients.\textsuperscript{15} Five cases showed diffuse growth; 2 showed an inverse follicular pattern.

On high power, NMZL cells show heterogeneous morphology, varying from centrocyte-like cells to monocytoid cells to plasmacytoid cells and plasma cells with varying numbers of interspersed centroblasts and immunoblasts. monocytoid cells have a central nucleus with condensed chromatin and indistinct nucleoli, surrounded by ample pale cytoplasm. Centrocyte-like cells, resembling the centrocytes of the germinal center, have nuclei with slightly irregular nuclear membranes and a coarser chromatin structure. Lymphoplasmacytoid cells have some, but not all features of plasma cells; in comparison to plasma cells they have less cytoplasm that is basophilic. They are smaller than typical ‘Marschalko-type’ plasma cells and have a finer chromatin structure. Monocytoid cells were reported in one-third of cases in one study,\textsuperscript{15} but predominance of monocytoid cells is rare and should prompt consideration of secondary lymph node involvement by MALT lymphoma.\textsuperscript{49} Plasmacytic differentiation has been reported in 22-47%\textsuperscript{13,15,48,50} and can be extensive (Figure 1G-I). Dutcher bodies are rarely observed, but can be numerous.\textsuperscript{12,49} One case of NMZL with Auer-rod-like inclusions has been reported.\textsuperscript{51}

**Table 1. Clinical characteristics.**

<table>
<thead>
<tr>
<th>N. M:F</th>
<th>Age (range)</th>
<th>Median 59 years</th>
<th>1:1.3 35% over 60 years</th>
<th>1:1.3 35% over 60 years</th>
<th>Mean 61 Median 50 years (13-79)</th>
<th>2.6:1 Median 50 years (27-83)</th>
<th>1:1.8 Median 64 years (29-83)</th>
<th>1:1.2 Median 64 years (29-83)</th>
<th>1:1.2 Median 64 years (29-83)</th>
<th>1:1.2 Median 64 years (29-83)</th>
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<tr>
<td>Stage at presentation ≤ III (%)</td>
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<td>68%</td>
<td>41%</td>
<td>47%</td>
<td>76%</td>
<td>77%</td>
<td>22%</td>
<td>59%</td>
<td>90%</td>
<td>69%</td>
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<tr>
<td>ECOG score ≤ 2 (%)</td>
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<td>NA</td>
<td>17%</td>
<td>15%</td>
<td>6%</td>
<td>6%</td>
<td>0%</td>
<td>43%</td>
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<td>95%</td>
<td>95%</td>
<td>NA</td>
<td>NA</td>
<td>98%</td>
<td>NA</td>
<td>NA</td>
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<tr>
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<td>10%</td>
<td>NA</td>
<td>24%</td>
<td>11%</td>
<td>NA</td>
<td>NA</td>
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</tr>
<tr>
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<td>5%</td>
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<td>24%</td>
<td>NA</td>
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<td>15%</td>
<td>6%</td>
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</tr>
<tr>
<td>HCV (%)</td>
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<td>NA</td>
<td>20%</td>
<td>5%</td>
<td>0%</td>
<td>24%</td>
<td>NA</td>
<td>NA</td>
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</tr>
</tbody>
</table>

Karnofsky score ≤ 70% in 0% of patients; Data not available for all patients. Percentages instead of number of patients indicated (for a subset of variables). NA: not available; ECOG: Eastern Cooperative Oncology Group; HCV: hepatitis C virus; LDH: lactate dehydrogenase.

-Haematologica | 2013; 98(7)
31%, respectively). The splenic and floral types were present in 11% and 14%, respectively.

A floral variant was also reported by Karube et al. in 6 cases of NMZL. These showed a proliferation of medium-sized cells in the marginal zone that surrounded enlarged germinal centers with a thick and irregular mantle zone that sometimes extended into the germinal center, similar to progressively transformed germinal centers. Rarely, NMZL with numerous epithelioid histiocytes, hyaline-vascular Castleman disease-like features, and NMZL in association with Rosai-Dorfman disease, light and heavy chain deposition disease, and non-lymphomatous skin lesions have been reported. The pattern of bone marrow infiltration has been described in only a small number of cases, with a nodular and paratrabecular pattern in most cases, followed by an interstitial pattern. One study reported intrasinusoidal growth, which was the sole pattern present in a single case.

The impact of centroblasts percentage on prognosis and the dividing line between DLBCL and NMZL remain unclear. Some authors diagnosed a case as being transformed if more than 20% of cells were centroblasts, which rendered a diagnosis of concurrent DLBCL in 20% of NMZL. Two other studies diagnosed DLBCL if more than 50% of tumor cells were centroblasts, which was present in 25% and 31%. Others have been more reluctant to diagnose transformation if large cells are still admixed with smaller tumor cells. In a study by Traverse-Glehen and colleagues, the presence of more than 20% of large cells had no significant effect on prognosis. However, as put forward by Kaur, these patients were mostly treated with aggressive chemotherapy, irrespective of large cell percentage. This could have prevented the detection of a significant effect of large cell per-
In our own practice, we diagnose transformation in NMZL only if sheets of large cells are present, similar to the criterion used in other lymphoma types (Figure 2).66

Immunophenotype
NMZL cells express pan B-cell markers including CD20, CD79a, and PAX5. The majority of cases are BCL2 positive, although numbers vary from 43% to 100% of cases.13,15,36,40,43,52 Most studies report no expression of BCL6, although one study describes BCL6 staining in a proportion of cells or large cells only in 43% of cases.15 CD10 positivity has been reported only rarely.54,67 CD5 and CD23 are usually negative, being reported in 0-17% and 0-29% of cases, respectively.13,15,48,52,54,68 Although studied in only few patients, the majority of NMZLs appear to express MUM1.13,15,54 CD43 expression varies between studies from 5-75%.13,48,52,54,69 DBA.44 expression has been reported in a subset of NMZLs in small studies.13,70 The germinal center markers HGAL and LMO2 are expressed only very rarely in NMZL; only one study reported expression of these markers in one of 18 and one of 5 cases, respectively.13,71 A larger study showed no expression of germinal center markers were excluded from the NMZL group.

The germinal center markers HGAL and LMO2 are expressed only very rarely in NMZL; only one study reported expression of these markers in one of 18 and one of 5 cases, respectively.13,71 A larger study showed no expression of HGAL and LMO2 in small studies.13,70 The germinal center markers HGAL and LMO2 are expressed only very rarely in NMZL; only one study reported expression of these markers in one of 18 and one of 5 cases, respectively.13,71 A larger study showed no expression of HGAL and LMO2 in small studies.13,70

Cytogenetics
Multiple studies have investigated the cytogenetic features of NMZL using classical cytogenetics, comparative genomic hybridization, and fluorescence in situ hybridization (FISH). Although numerous cytogenetic abnormalities have been reported, no specific alterations have been identified so far. Figure 3 summarizes gains and losses of chromosome regions and whole chromosomes reported in the literature.12,15,36,76-86 Gains of chromosome 1q, 2p, 3p, 3q, 6p, and 6q are most frequent, as are losses of 1q and 6q. Chromosomes 3, 12, and 18 most often show trisomy. Monosomy is more rarely observed and most frequently involves chromosomes 9, 13, and 14.

Multiple translocations have been reported in NMZL, but they do not share a common breakpoint region. This is in contrast to MALT lymphomas, which frequently have translocations involving API2, MALT1, BCL10, and FOXP1. The translocations that have been described in NMZL do not include regions harboring these genes.12,15,36,77-80 Although Dierlamm and colleagues did not detect translocations involving BCL6 in NMZL, Traverse-Glehen et al. do suggest translocations involving BCL6.15

Molecular features
Gene expression studies in NMZL have generated different results. One study of 16 NMZL and 8 FL cases identified MNDAs as a gene that is differentially expressed between FL and NMZL, with a rather low ranking of genes that are known to be expressed more often in FL than NMZL (e.g. CD10, BCL6).75 Another study of 15 NMZLs and 16 FLs reported a rather homogeneous gene expression profile in NMZLs resembling marginal zone and memory B cells.86 Compared to FL, NMZL showed overexpression of NF-kB-related and -binding genes.
(TRAF4, CD82), IL-32, histones, members of the TNF family (TACI, TNFRSF14), and genes involved in lymphocyte activation (TGFBI). FLs showed higher expression of germinal center markers (CD10, BCL6, GCET1, LMO2) in comparison to NMZL. This study also examined microRNA profiles; NMZL showed increased expression of miR-221, miR-223, and let-7f. In FLs, strong expression of miR-494 was observed. Activation of the NF-κB pathway is a known feature of extranodal MZL, which is frequently a result of specific translocations or mutations in NF-κB inhibitors. As discussed above, recurrent NF-κB activating translocations are not a feature of NMZL, but inactivating mutations of TNFAIP3, an inhibitor of the NF-κB pathway, have been shown in 3 of 9 cases of NMZL in one study.91 This is an interesting finding with potential diagnostic utility, but needs confirmation in larger studies.

To summarize, there is variability in morphology, phenotype, and molecular profile that may be due to either the variability of the disease itself, or to the variability of the criteria used for the diagnosis.

Differential diagnosis

Reactive conditions

Toxoplasmosis and human immunodeficiency virus (HIV)-associated lymphadenopathy can show hyperplasia of monocyteid B cells. Morphological differentiation from NMZL can be difficult in some cases. Immunohistochemistry can be helpful; normal monocyteid B cells are BCL2 negative whereas NMZL cells are usually BCL2 positive.69,92 If a final diagnosis cannot be made by morphology and immunohistochemistry, clonality testing can provide important additional information.93

Follicular lymphoma

The classical case of FL is easily distinguished from NMZL, but areas of overlap exist. First, some FLs grow in a marginal zone pattern resembling NMZL. In addition, NMZLs frequently show follicular colonization that can cause resemblance to FL. In follicular colonization, the lymph node retains a nodular architecture on low power. The BCL2 positive NMZL cells that infiltrate the germinal center are positive for BCL6 and GCET1, whereas FL cells are negative.58

Figure 3. Cytogenetics. Overview of cytogenetic abnormalities in NMZL. (A) Overview of chromosomal gains (top, in green) and losses (bottom, in red). Results for the small arm (p, left) and long arm (q, right) are indicated separately. (B) Overview of trisomies (top, green) and monosomies (bottom, red). Results represent an aggregation of data from multiple studies, comprising 100 patients.12,15,36,76-83,85,86 For most patients (n=75), all detected karyotypic abnormalities were reported. In one CGH study with 25 patients, only recurrent gains (in ≥4 cases) were reported.81 For monosomies and trisomies of chromosomes 3, 7, and 12, an additional study of 12 patients has been included.84

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Figure 3. Cytogenetics.
centers falsely suggest BCL2-positive follicles. The residual follicular cells in the background give a false impression of BCL6- and CD10-positivity. Accordingly, an erroneous diagnosis of FL is easily made. The key to solving this problem lies in careful review at high power which shows BCL2-negative centroblasts and centrocytes that express BCL6 and CD10, with the truly neoplastic BCL2-positive cells in between (Figure 4). Another clue for the presence of pre-existent rather than neoplastic germinal centers comes from a high proliferative index as shown by immunohistochemistry for Ki-67.

In the majority of cases, demonstration of a translocation involving BCL2 will help in diagnosing FL, but approximately 10% of FLs do not have this translocation. At present there are no good criteria by which t(14;18) negative follicular lymphoma can be separated from NMZL with complete follicular colonization. Therefore, in some cases, a definitive diagnosis cannot be made. New immunohistochemical markers could further reduce this ambiguous group (also discussed under “Immunophenotype”).

LMO2 and HGAL are germinal center markers that are frequently positive in FL. MNDA and IRTA have recently been identified as markers of MZL, although both have only been reported in single studies (see above). With flow cytometry, the junctional adhesion molecule C (JAM-C) has been shown to be expressed in the large majority of MZLs, but not in FLs. This is a potentially interesting finding, although it needs confirmation in larger studies with specification of the specific subtypes of MZL.

Extranodal marginal zone lymphoma

By definition, the distinction of NMZL from lymph node involvement by EMZL must be made by a thorough clinical search for extranodal disease (Figure 5A and B). However, some features suggest a primary extranodal lymphoma. Pure monocytoid morphology is more typical of MALT lymphoma than NMZL. In addition, EMZL frequently have specific translocations involving BCL10 and MALT1, which have not been reported in NMZL.

Splenic MZL (SMZL) only rarely presents with lymphadenopathy. It virtually always infiltrates the bone marrow with a characteristic intertrabecular and intrasinusoidal pattern, which is not typical of NMZL (Figure 5C and D). IgD negativity is an argument against SMZL. Approximately 40% of splenic MZLs have a loss of chromosome 7q, which is present in less than 5% of NMZLs.

Lymphoplasmacytic lymphoma

NMZL and lymphoplasmacytic lymphoma (LPL) are both low-grade B-cell lymphomas with a morphology ranging from lymphocytes to plasma cells, making distinction between these entities problematic in some cases. Again, it is important to take clinical features into account; LPL generally presents in the bone marrow with hyperviscosity (Waldenström macroglobulinemia), whereas NMZL generally present with lymphadenopathy. However, especially in lymph nodes, differentiation can be difficult or impossible. Arguments in favor of NMZL include monocytoid cellular morphology, a marginal zone growth pattern, and follicular colonization. LPL classically shows (partial) retention of the architecture with dilated sinuses, although other patterns frequently occur. We feel that the use of three diagnostic categories (i.e. NMZL, LPL, and ambiguous: low-grade B-cell lymphoma with plasmacytic differentiation) is a sensible approach to this diagnostic problem. The recent discovery of L265P hotspot mutations in MYD88 in the large majority of LPLs but not in MZLs is of great potential use for the differential diagnosis between LPL and NMZL. This is illustrated by a case we had classified as NMZL but was shown to carry a L265P mutation in MYD88. Subsequent evaluation indeed revealed clinical features of Waldenström macroglobulinemia leading to a diagnosis of LPL rather than NMZL.

Other B-cell lymphomas

Mantle cell lymphoma sometimes resembles NMZL
morphologically. It can be reliably distinguished from NMZL by its positivity for CD5 and cyclin D1, and the presence of a CCND1 translocation. Similarly, chronic lymphocytic leukemia differs from NMZL by its expression of CD5 and CD23.

NMZL frequently contains significant numbers of centroblasts, which can cause confusion with diffuse large B-cell lymphoma (DLBCL). A clear boundary between NMZL and DLBCL has not been established. In our own practice, we only diagnose transformation to DLBCL if sheets of blasts are present without interspersed smaller tumor cells.

Pediatric nodal marginal zone lymphoma

In 2003, Taddese-Heath and colleagues recognized a pediatric subtype of NMZL. Characteristic features were a striking male predominance and an indolent disease course. In contrast to NMZL in adults, pediatric NMZLs presented with only localized disease, corresponding with an excellent prognosis. Of note, ‘pediatric NMZL’ might also occur in (young) adults; patients up to 44 years of age have been reported. Histologically, pediatric NMZL was frequently associated with progressively transformed germinall center-like changes (in 66%), which is not a feature of adult NMZL. Cytogenetic abnormalities that characterize adult EMZL have only been rarely observed in pediatric MZL, with trisomy 18 and trisomy 3 as the most frequent aberrations. There are no data regarding the expression of IRTA1 and MNDA. Based on these features, it seems relevant to keep the pediatric lesions separate from adult NMZL, and to try to find markers for both.

Treatment and prognosis

There is currently no consensus on how to treat NMZL patients. Usually, guidelines for follicular lymphoma or chronic lymphocytic leukemia/ small lymphocytic lymphoma are adopted. Different studies have reported different (combinations of) treatments, including watchful waiting, surgery, radiotherapy, different chemotherapeutic regimens, rituximab, and autologous stem cell transplantation. However, no optimal treatment strategy can be deduced from these studies. Complete response is achieved in 55-74% of patients.

A phase II study in 26 patients with marginal zone lymphomas, mostly NMZLs, illustrated that treatment regimens in other low-grade B-cell lymphomas cannot be simply applied to MZL. Although treatment with fludarabine and rituximab was highly effective, it came with significant toxicity that had not been observed in other lymphoma types to that extent.

Five-year overall survival rates range from 64-89%. The FLIPI (Follicular Lymphoma International Prognostic Index) has been reported to predict overall survival and progression-free survival for patients with NMZL, but this could not be confirmed for the NMZL subgroup in a recent study with 32 NMZL patients. Age, the presence of B symptoms, Ann Arbor stage, anemia, performance score, sex, race, and chemotherapy were associated with progression-free survival or event-free survival in multivariate analyses.

It is clear that a better understanding of this lymphoma type is needed in order to select these patients for newer, targeted therapies and to improve outcome.

Conclusions and recommendations

Nodal marginal zone lymphoma remains an enigmatic entity with accompanying difficulties in diagnosis and a lack of knowledge of prognosis and treatment. Because of its rarity, it is hard to obtain large study groups. Also, because NMZL is frequently a diagnosis of exclusion, the series that have been studied might contain a somewhat heterogeneous group of low-grade B-cell lymphomas. Nevertheless, progress is being made; recent studies have identified positive markers for MZL (i.e. MNDA and IRTA1), and gene expression studies have identified a spe-
specific gene expression profile that separates NMZL from other lymphoma types.

In routine practice, the diagnosis of NMZL can be established on the basis of the criteria described above and by excluding other lymphoma entities. As we have indicated, in some cases, this probably results in misdiagnosis; not a big problem since prognosis and treatment are quite similar. However, as more and more targeted treatments are becoming available, better knowledge of the pathogenesis of NMZL will be necessary to determine which targeted pharmaceuticals will be of benefit to affected patients.

To improve understanding of this disease, series that are under investigation for pathological criteria and clinical features will need very rigorous exclusion of cases, including molecular testing and inclusion of complete clinical data. By doing that, the group of cases in a study may become rather small, but there will be a greater chance of finding relevant new data.

**Authorship and Disclosures**

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