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 articles 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".[1] 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.[2] 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).[3] 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.[4,5] In the REAL classification of 1994, and in the 2001 WHO classification, NMZL was adopted as a provisional entity.[6,7] 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.[8]

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Epidemiology and etiology

NMZL is a rare lymphoma, accounting for 1.5-1.8% of lymphoid neoplasms.[9,10] 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.[9-20] 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 lymphoma in an axillary lymph node. However, we detected *H. pylori* by PCR analysis and a gastric biopsy revealed EMZL. 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, monocytoid 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.[16] 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),[13,14] but other studies did not.[15] The study by Camacho *et al.* also showed HBV infection in 30% 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.[22-25]

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.[26,27]

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.[13,15,28-31] Preferential use of VH3-34 is associated with Epstein-Barr virus and cytomegalovirus in patients with chronic lymphocytic leukemia.[32] In NMZL, an association with these viruses has not been established.[13,33,34] 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.[16-18] 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.[9-11,13-19] 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%).[9,14-16,18] 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.[15] Involvement of the peripheral blood is reported in 10-24% of patients.[9,13,15,16] 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.[9,10,13-18,38]

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).[39,40]

Serum lactate dehydrogenase (LDH) is elevated in 12-48% of patients, beta 2 (β2)-microglobulin is increased in 29-45%.[9,10,13-19] An M-component is present in 6-33% of patients.[9,15-17] In one study, cryoglobulins were present in only 2 of 14 patients.[15] Hypoalbuminemia was reported in 7-10% in two studies.[9,15]

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 physiological 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%),[13,15,28-31,42] 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.[30] 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

Table 1. Clinical characteristics.

	Nathwani[10] *et al.* 1999[c]	Berger[9] *et al.* 2000	Camacho[13] *et al.* 2003	Oh[14] *et al.* 2006	Traverse-Glehen[15] *et al.* 2006	Arcaini[16] *et al.* 2007[c]	Kojima[17] *et al.* 2007	Mazloom[18] *et al.* 2010	Heilgeist[19] *et al.* 2013	Olszewski[11] *et al.* 2013
N.	20	37	27	36	21	47	65	27	32	4724
M:F	1:1.3	1:1.3	1:1.7	2.6:1	2:1	1:1.8	1:1.2	1:1.7	1.67:1	1:1.12
Age (range)	Median 59 years	35% over 60 years	Mean 61 years (26-92)	Median 50 years (13-79)	Median 54 years (27-83)	Median 63 years	Median 64 years (29-83)	56	Median 67 years (38-88)	Median 69 years
Stage at presentation ≥ III (%)	71	68	41[b]	47[b]	76	77	22	59	90[b]	69[b]
ECOG score ≥2 (%)	NA[a]	13[b]	NA	17	15[b]	6	6	0	43[b]	NA
Peripheral lymphadenopathy (%)	100	95	95[b]	NA	NA	98	NA	NA	NA	NA
Cervical lymphadenopathy (%)	81	11	NA	56	71	53	86	NA	NA	NA
B symptoms (%)	14	14	NA	8	10	15	8	8[b]	NA	25[b]
Bone marrow involvement (%)	28	43[b]	29[b]	21[b]	62	45	0	30	NA	NA
Bulky tumor (%)	31	17[b]	NA	NA	NA	11	NA	NA	NA	NA
Anemia (hemoglobin< 120g/L) (%)	NA	31[b]	NA	36	24	11	NA	30	NA	NA
Peripheral blood involvement (%)	NA	11	10[b]	NA	24	11	NA	NA	NA	NA
LDH elevation	36	40[b]	43[b]	20[b]	48	15	12	22	35[b]	NA
β_2-microglobulin elevated (%)	NA	33[b]	41[b]	NA	29	45	NA	38	NA	NA
M-protein (%)	NA	8	NA	NA	33	15	6	NA	NA	NA
HCV (%)	NA	NA	20[b]	5[b]	0	24[b]	NA	NA	NA	NA

[a]Karnofsky score ≤70% in 0% of patients; [b]Data not available for all patients. [c]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.

and X-linked lymphoproliferative disorder, who lack functional germinal centers, but do show some SHM.[43,44] Multiple other studies have also shown germinal center-independent SHM.[45,46] Very recently, Warsame and associates showed evidence of ongoing mutations in microdissected monocytoid B cells.[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 MNDA 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.[48] In their study, a diffuse pattern of infiltration was most frequent (in 31 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 *et al.* of 21 patients, nodular and interfollicular growth was most frequently observed, both in one-third of patients.[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,[15] but predominance of monocytoid cells is rare and should prompt consideration of secondary lymph node involvement by MALT lymphoma.[49] Plasmacytic differentiation has been reported in 22-47%[13,15,48,50] and can be extensive (Figure 1G-I). Dutcher bodies are rarely observed, but can be numerous.[15,50] One case of NMZL with Auer-rod-like inclusions has been reported.[51]

Campo *et al.* classified growth patterns in NMZL into splenic and MALT type, which has subsequently become the subject of debate.[52,53] The splenic type, being present in 6 of 36 cases, was described as consisting of a polymorphic infiltrate around residual germinal centers that lack a clear mantle cuff. The remainder of the cases were of the MALT type, characterized by perisinusoidal and perivascular infiltration of monocytoid and centrocytoid cells next to residual germinal centers with a well-preserved mantle cuff. Splenic type NMZLs were IgD positive, a feature that was confirmed in some studies,[13,54] but not in others.[17,48] Unfortunately, not all these studies reported IgD expression, and it was not reported in relation to growth pattern.[13]

Kojima *et al.* adopted yet another morphological scheme which recognized a splenic type, MALT type, floral type, and diffuse large B-cell lymphoma (DLBCL) + MALT type.[17] In their study of 65 patients, the MALT and DLBCL+MALT type were most frequent (in 45% and

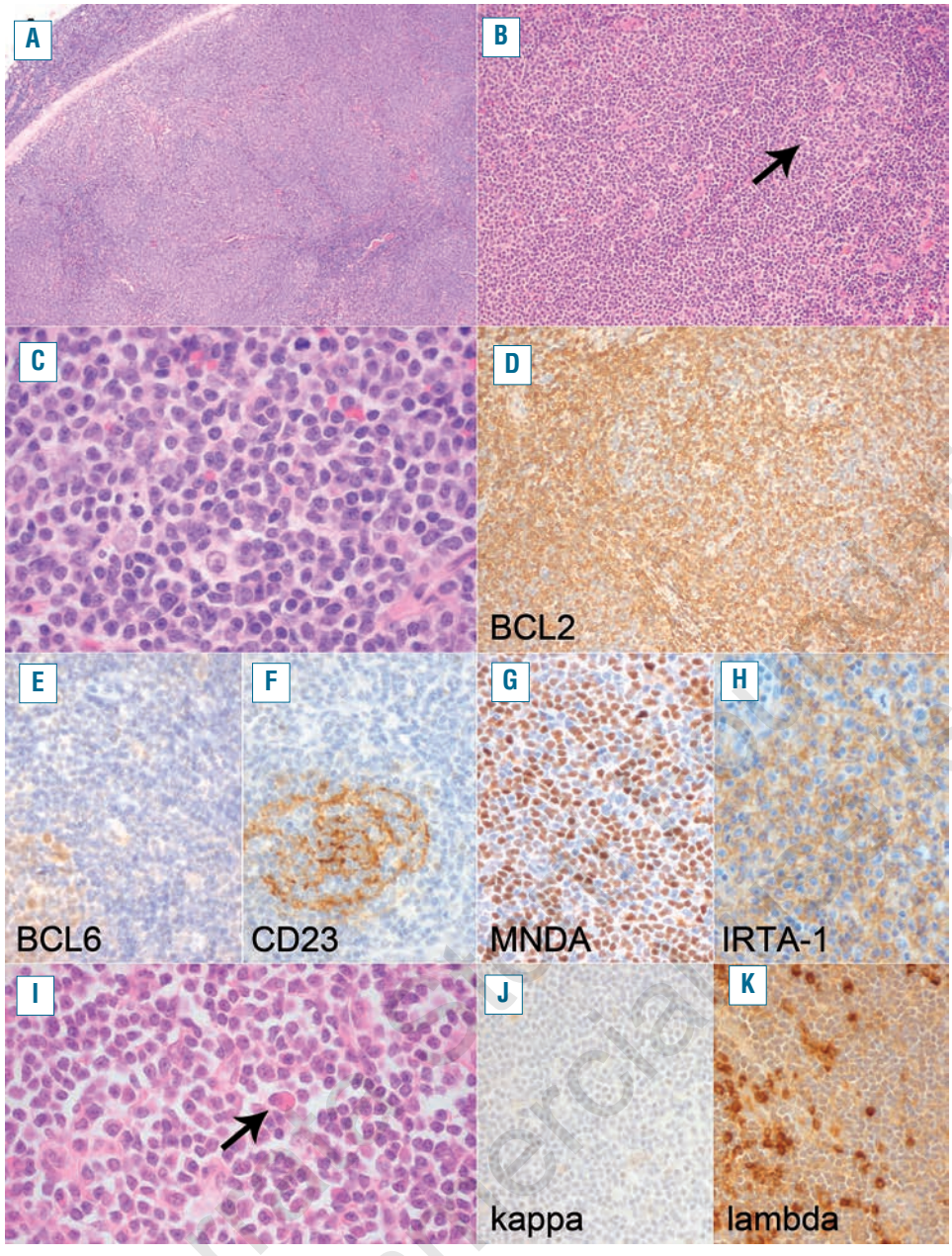

Figure 1. NMZL histology. (A-C). Hematoxylin and eosin stain, showing a nodular architecture on low power (A), with recognizable remnant follicles at higher power (arrow) (B). In this case, the lymphoma cells consist of small cells with scant cytoplasm and round to indented nuclei with fine chromatin structure (lymphocytic/ centrocytic) (C). Immunohistochemistry shows BCL2-negative remnant follicles surrounded by BCL2-positive lymphoma cells. (D). BCL6 highlights the remnant follicles (E). CD23 shows dendritic networks that have been partially destroyed. (F) The tumor cells show strong expression of MNDA (G). (H) Strong expression of IRTA-1 in another case of NMZL. (I-K) Another case of NMZL with prominent plasma cell differentiation, with Russell bodies (arrow) (I). Immunohistochemistry against immunoglobulin light chains kappa and lambda reveals light chain restriction for lambda light chains (J-K).

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.[33] 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.[55-60] 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.[15,38,61] One study reported intrasinusoidal growth, which was the sole pattern present in a single case.[38]

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 NMZLs.[10,62] Two other studies diagnosed DLBCL if more than 50% of tumor cells were centroblasts, which was present in 25% and 31%.[9,17] Others have been more reluctant to diagnose transformation if large cells are still admixed with smaller tumor cells.[16,63,64] In a study by Traverse-Glehen and colleagues, the presence of more than 20% of large cells had no significant effect on prognosis.[15] However, as put forward by Kaur, these patients were mostly treated with aggressive chemotherapy, irrespective of large cell percentage.[65] This could have prevented the detection of a significant effect of large cell per-

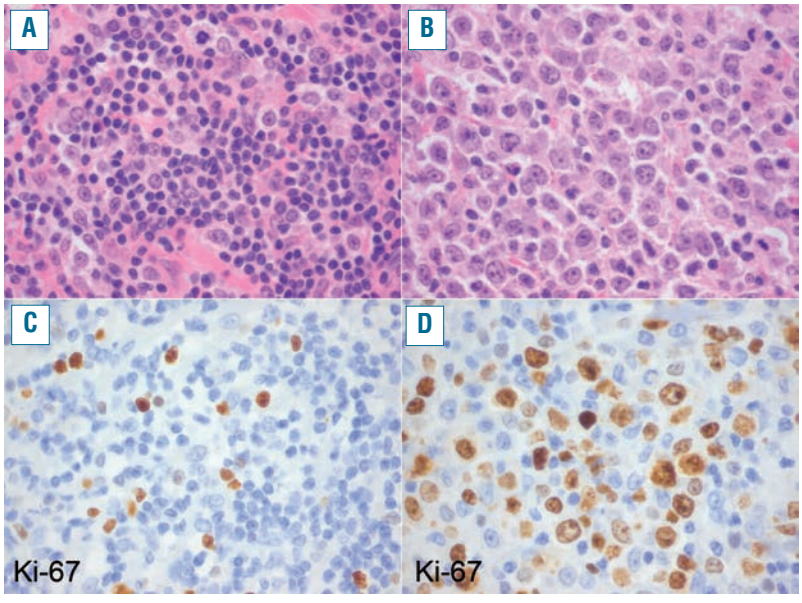

Figure 2. NMZL with transformation to diffuse large B-cell lymphoma (DLBCL). (A) Low-grade component, showing mainly small lymphocytic cells with scattered histiocytes and only rare large cells. (B) High-grade component in the same lymph node, consisting mainly of large cells that are arranged in sheets, indicating transformation to DLBCL. (C-D) Ki-67 immunohistochemistry shows low proliferative activity in the low-grade component (C), and high proliferative activity in the high-grade component (D).

centage. 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.[13,15,33,48,52,54] 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] One study detected cyclin D1 expression in 2 of 24 cases, but only in scattered cells and with a lower intensity than in mantle cell lymphoma.[52] Other studies showed no cyclin D1 expression.[13,48,54,69] 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.[71] A larger study showed no expression in 43 cases,[48] but in this study, cases with expression of germinal center markers were excluded from the NMZL group.

Recently, new positive markers for marginal zone cells have been reported that could help in the diagnosis of NMZL. Myeloid cell nuclear differentiation antigen (MNDA) is expressed by cells of the myelomonocytic lineage, but has also been shown to be expressed by a B-cell subset that is located around the germinal center and interfollicular regions.[72] Accordingly, a recent study showed frequent MNDA expression in NMZL (in 75%), but only rarely (in 5%) in follicular lymphoma (FL).[73]

In a similar way, immunoglobulin superfamily receptor translocation-associated 1 (IRTA1) was shown to be expressed on marginal zone and monocytoid B cells,[74] and also subsequently on MZLs.[75] In the latter study, 73% of NMZLs were IRTA1-positive in contrast to none of 320 FLs.

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.[12,15,76,77,79,82,85-89] Although Dierlamm and colleagues did not detect translocations involving *BCL6* in NMZL,[12,20,77] the karyotypes of 3 of 21 patients described by 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 MNDA 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).[73] Another study of 15 NMZLs and 16 FLs reported a rather homogeneous gene expression profile in NMZLs resembling marginal zone and memory B cells.[90] Compared to FL, NMZL showed overexpression of NF-κB-related and -binding genes

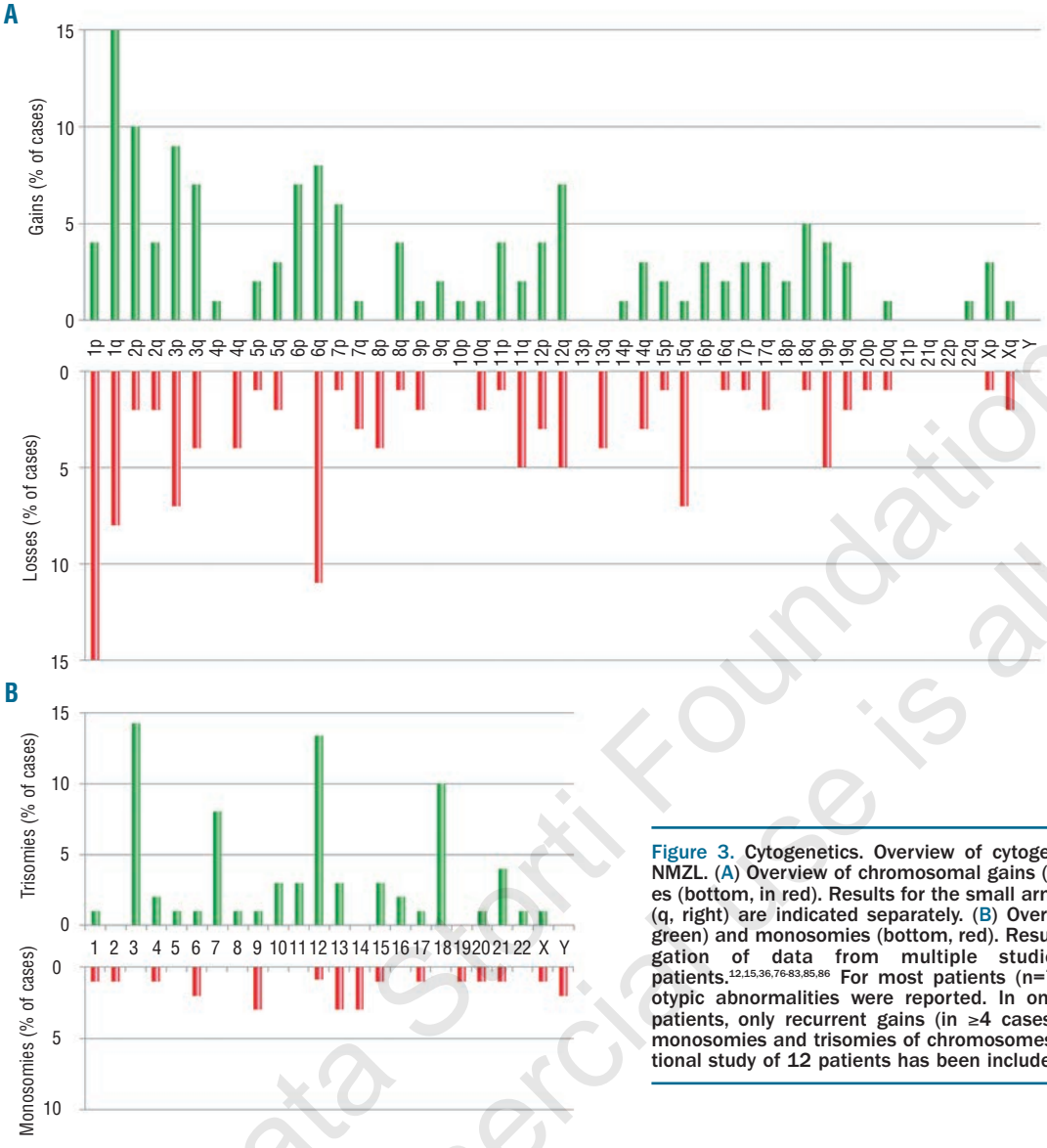

Figure 3. Cytogenetics. Overview of cytogenetic abnormalities in NMZL. (A) Overview of chromosomal gains (top, in green) and losses (bottom, in red). Results for the small arm (p, left) and long arm (q, right) are indicated separately. (B) Overview of trisomies (top, green) and monosomies (bottom, red). 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]

(TRAF4, CD82), IL-32, histones, members of the TNF family (TACI, TNFRSF14), and genes involved in lymphocyte activation (TGFB1). 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 monocytoid B cells. Morphological differentiation from NMZL can be difficult in some cases. Immunohistochemistry can be helpful; normal monocytoid 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

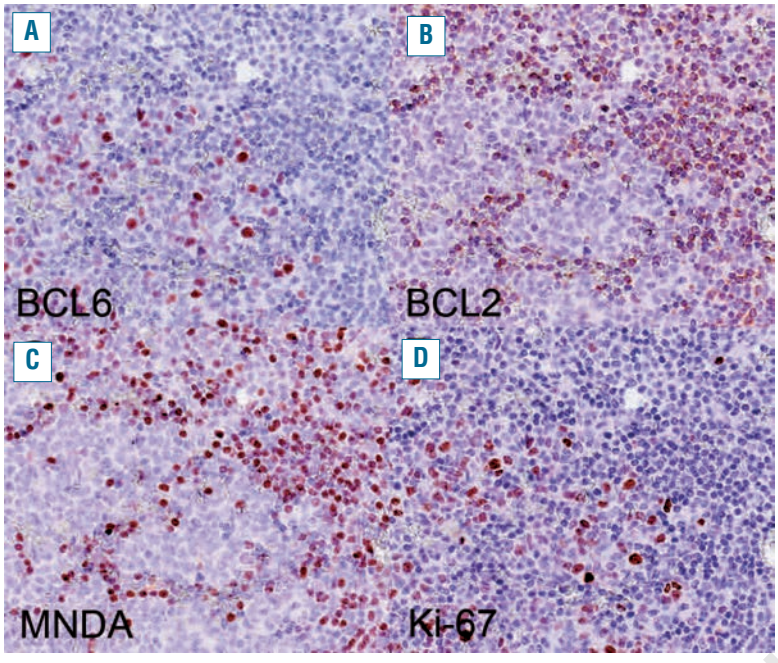

Figure 4. Follicular colonization. A single section was sequentially stained with multiple antibodies, allowing assessment of the expression of multiple proteins in the same section. (A) A pre-existent germinal center is present in the bottom-left corner, which is highlighted by BCL6 staining. (B) The germinal center cells are BCL2 negative, whereas the infiltrating lymphoma cells are BCL2 positive. (C) MNDA expression largely overlaps with BCL2 expression, confirming that indeed the lymphoma cells are the BCL2 positive cells. (D) Ki-67 highlights the pre-existent germinal center similar to the BCL6 stain, indicating that the proliferative activity is high in the germinal center cells, but low in lymphoma cells.

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.[94]

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 (Waldenströms 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.[95] 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 Waldenströms macroglobulinemia leading to a diagnosis of LPL rather than NMZL.

Other B-cell lymphomas

Mantle cell lymphoma sometimes resembles NMZL

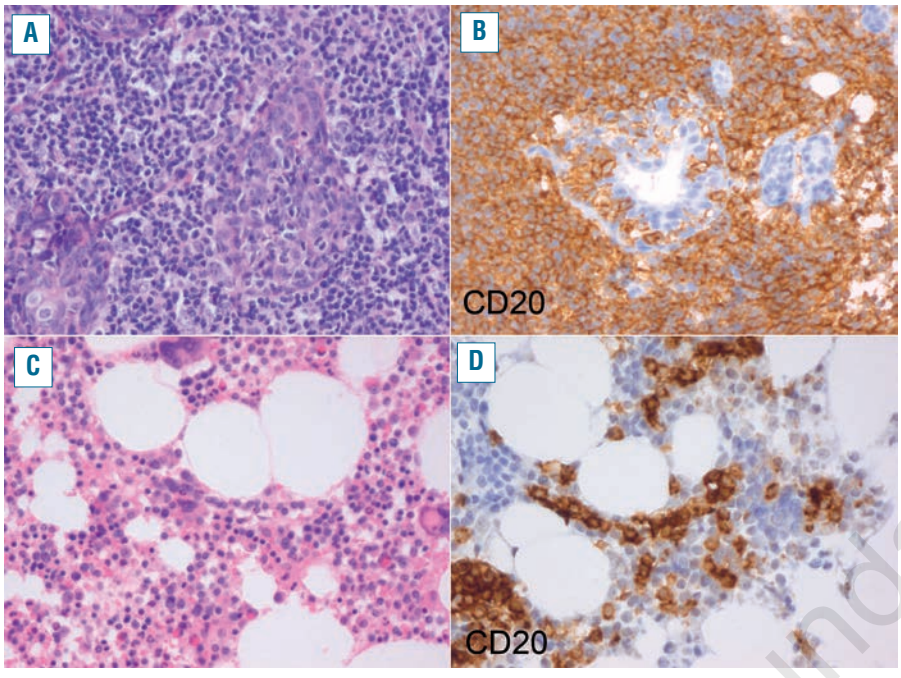

Figure 5. Extranodal and splenic marginal zone lymphoma. (A and B). Extranodal marginal zone lymphoma of the parotid gland, showing the typical lymphoepithelial lesions; hematoxylin and eosin stain shows infiltration and destruction of glandular epithelium (A), which is highlighted by immunohistochemical staining of lymphoma cells with anti-CD20 (B). (C and D): bone marrow involvement of splenic marginal zone lymphoma. Hematoxylin and eosin stain shows scattered strands of lymphoid cells in a background of pre-existent hematopoiesis (C). The typical sinusoidal pattern of infiltration is highlighted by CD20 staining (D), which shows strands of lymphoid cells with a somewhat rounded contour.

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.[96] 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.[97] Histologically, pediatric NMZL was frequently associated with progressively transformed germinal 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.[98] 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.[99] Different studies have reported different (combinations of) treatments, including watchful waiting, surgery, radiotherapy, different chemotherapeutic regimens, rituximab, and autologous stem cell transplantation.[9,13-19] However, no optimal treatment strategy can be deduced from these studies. Complete response is achieved in 55-74% of patients.[9,14-18]

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.[100] 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%.[11,14-19] The FLIPI (Follicular Lymphoma International Prognostic Index) has been reported to predict overall survival[16] and progression-free survival[14] for patients with NMZL, but this could not be confirmed for the NMZL subgroup in a recent study with 32 NMZL patients.[19] 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.[11,14,16]

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-

cific 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 being investigated 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

Information on authorship, contributions, and financial & other disclosures was provided by the authors and is available with the online version of this article at www.haematologica.org.

References

1. Swerdlow SH, Campo E, Harris NL, Jaffe ES, Pileri SA, Stein H, et al. WHO classification of tumours of haematopoietic and lymphoid tissues. Lyon: International Agency for Research on Cancer; 2008.
2. Sheibani K, Sohn CC, Burke JS, Winberg CD, Wu AM, Rappaport H. Monocytoid B-cell lymphoma. A novel B-cell neoplasm. Am J Pathol. 1986;124(2):310-8.
3. Lennert K, Feller AC. Histopathologie der Non-Hodgkin-Lymphome: Nach der aktualisierten Kiel-Klassifikation (Based on the Updated Kiel Classification). Berlin Heidelberg: Springer; 1990.
4. Nizze H, Cogliatti SB, von Schilling C, Feller AC, Lennert K. Monocytoid B-cell lymphoma: morphological variants and relationship to low-grade B-cell lymphoma of the mucosa-associated lymphoid tissue. Histopathology. 1991;18(5):403-14.
5. Ortiz-Hidalgo C, Wright DH. The morphological spectrum of monocytoid B-cell lymphoma and its relationship to lymphomas of mucosa-associated lymphoid tissue. Histopathology. 1992;21(6):555-61.
6. Harris NL, Jaffe ES, Stein H, Banks PM, Chan JK, Cleary ML, et al. A revised European-American classification of lymphoid neoplasms: a proposal from the International Lymphoma Study Group. Blood. 1994;84(5):1361-92.
7. Jaffe ES, Harris NL, Stein H, Vardiman JW. World Health Organisation Classification of Tumours. Pathology and Genetics of Tumours of Haematopoietic and Lymphoid Tissues. Lyon: IARC Press; 2001.
8. Oh SY, Kim WS, Kim JS, Kim SJ, Lee S, Lee DH, et al. Waldeyer's ring marginal zone B cell lymphoma: are the clinical and prognostic features nodal or extranodal? A study by the Consortium for Improving Survival of Lymphoma (CISL). Int J Hematol. 2012;96(5):631-7.
9. Berger F, Felman P, Thieblemont C, Pradier T, Baseggio L, Bryon PA, et al. Non-MALT marginal zone B-cell lymphomas: a description of clinical presentation and outcome in 124 patients. Blood. 2000;95(6):1950-6.
10. Nathwani BN, Anderson JR, Armitage JO, Cavalli F, Diebold J, Drachenberg MR, et al. Marginal zone B-cell lymphoma: A clinical comparison of nodal and mucosa-associated lymphoid tissue types. Non-Hodgkin's Lymphoma Classification Project. J Clin Oncol. 1999;17(8):2486-92.
11. Olszewski AJ, Castillo JJ. Survival of patients with marginal zone lymphoma: Analysis of the Surveillance, Epidemiology, and End Results database. Cancer. 2013;119(3):629-38.
12. Dierlamm J, Pittaluga S, Wlodarska I, Stul M, Thomas J, Boogaerts M, et al. Marginal zone B-cell lymphomas of different sites share similar cytogenetic and morphologic features. Blood. 1996;87(1):299-307.
13. Camacho FI, Algara P, Mollejo M, Garcia JF, Montalban C, Martinez N, et al. Nodal marginal zone lymphoma: a heterogeneous tumor: a comprehensive analysis of a series of 27 cases. Am J Surg Pathol. 2003;27(6):762-71.
14. Oh SY, Ryoo BY, Kim WS, Kim K, Lee J, Kim HJ, et al. Nodal marginal zone B-cell lymphoma: Analysis of 36 cases. Clinical presentation and treatment outcomes of nodal marginal zone B-cell lymphoma. Ann Hematol. 2006;85(11):781-6.
15. Traverse-Glehen A, Felman P, Callet-Bauchu E, Gazzo S, Baseggio L, Bryon PA, et al. A clinicopathological study of nodal marginal zone B-cell lymphoma. A report on 21 cases. Histopathology. 2006;48(2):162-73.
16. Arcaini L, Paulli M, Burcheri S, Rossi A, Spina M, Passamonti F, et al. Primary nodal marginal zone B-cell lymphoma: clinical features and prognostic assessment of a rare disease. Br J Haematol. 2007;136(2):301-4.
17. Kojima M, Inagaki H, Motoori T, Itoh H, Shimizu K, Tamaki Y, et al. Clinical implications of nodal marginal zone B-cell lymphoma among Japanese: study of 65 cases. Cancer Sci. 2007;98(1):44-9.
18. Mazloom A, Medeiros LJ, McLaughlin PW, Reed V, Cabanillas FF, Fayad LE, et al. Marginal zone lymphomas: factors that affect the final outcome. Cancer. 2010;116(18):4291-8.
19. Heilgeist A, McClanahan F, Ho AD, Witzens-Harig M. Prognostic value of the Follicular Lymphoma International Prognostic Index score in marginal zone lymphoma: An analysis of clinical presentation and outcome in 144 patients. Cancer. 2013;119(1):99-106.
20. Dierlamm J, Pittaluga S, Stul M, Wlodarska I, Michaux L, Thomas J, et al. BCL6 gene rearrangements also occur in marginal zone B-cell lymphoma. Br J Haematol. 1997;98(3):719-25.
21. Zuckerman E, Zuckerman T, Levine AM, Douer D, Gutekunst K, Mizokami M, et al. Hepatitis C virus infection in patients with B-cell non-Hodgkin lymphoma. Ann Intern Med. 1997;127(6):423-8.
22. Mele A, Pulsoni A, Bianco E, Musto P, Szklo A, Sanpaolo MG, et al. Hepatitis C virus and B-cell non-Hodgkin lymphomas: an Italian multicenter case-control study. Blood. 2003;102(3):996-9.
23. Nieters A, Kallinowski B, Brennan P, Ott M, Maynadie M, Benavente Y, et al. Hepatitis C and risk of lymphoma: results of the European multicenter case-control study EPILYMPH. Gastroenterology. 2006;131(6):1879-86.
24. Leleu X, O'Connor K, Ho AW, Santos DD, Manning R, Xu L, et al. Hepatitis C viral infection is not associated with Waldenstrom's macroglobulinemia. Am J Hematol. 2007;82(1):83-4.
25. Veneri D, Aqel H, Franchini M, Meneghini V, Krampera M. Prevalence of hepatitis C virus infection in IgM-type monoclonal gammopathy of uncertain significance and Waldenstrom macroglobulinemia. Am J Hematol. 2004;77(4):421.
26. Baraboutis IG, Marinos L, Lekakis LJ, Papastamopoulos V, Georgiou O, Tsagalou EP, et al. Long-term complete regression of nodal marginal zone lymphoma transformed into diffuse large B-cell lymphoma with highly active antiretroviral therapy alone in human immunodeficiency virus infection. Am J Med Sci. 2009;338(6):517-21.
27. Abella E, Besses C, Barranco C, Pedro C, Buch J, Espinet B. Nodal marginal zone lymphoma in AIDS patients: a casual association? AIDS. 2002;16(16):2232-4.
28. Tierens A, Delabie J, Pittaluga S, Driessen A, DeWolf-Peeters C. Mutation analysis of the rearranged immunoglobulin heavy chain genes of marginal zone cell lymphomas indicates an origin from different marginal zone B lymphocyte subsets. Blood. 1998;91(7):2381-6.
29. Miranda RN, Cousar JB, Hammer RD, Collins RD, Vnencak-Jones CL. Somatic mutation analysis of IgH variable regions reveals that tumor cells of most parafollicular (monocytoid) B-cell lymphoma, splenic marginal zone B-cell lymphoma, and some hairy cell leukemia are composed of memory B lymphocytes. Hum Pathol. 1999;30(3):306-12.
30. Conconi A, Bertoni F, Pedrinis E, Motta T, Roggero E, Luminari S, et al. Nodal marginal zone B-cell lymphomas may arise from different subsets of marginal zone B lymphocytes. Blood. 2001;98(3):781-6.
31. Marasca R, Vaccari P, Luppi M, Zucchini P, Castelli I, Barozzi P, et al. Immunoglobulin gene mutations and frequent use of VH1-69 and VH4-34 segments in hepatitis C virus-positive and hepatitis C virus-negative nodal marginal zone B-cell lymphoma. Am J Pathol. 2001;159(1):253-61.
32. Kostareli E, Hadzidimitriou A, Stavroyianni

N, Darzentas N, Athanasiadou A, Gounari M, et al. Molecular evidence for EBV and CMV persistence in a subset of patients with chronic lymphocytic leukemia expressing stereotyped IGHV4-34 B-cell receptors. Leukemia. 2009;23(5):919-24.
33. Karube K, Ohshima K, Tsuchiya T, Yamaguchi T, Kawano R, Suzumiya J, et al. A "floral" variant of nodal marginal zone lymphoma. Hum Pathol. 2005;36(2):202-6.
34. Chang KL, Chen YY, Weiss LM. Lack of evidence of Epstein-Barr virus in hairy cell leukemia and monocytoid B-cell lymphoma. Hum Pathol. 1993;24(1):58-61.
35. Chan CH, Hadlock KG, Foung SK, Levy S. V(H)1-69 gene is preferentially used by hepatitis C virus-associated B cell lymphomas and by normal B cells responding to the E2 viral antigen. Blood. 2001;97(4):1023-6.
36. Banerjee SS, Harris M, Eyden BP, Radford JA, Harrison CJ, Mainwaring AR. Monocytoid B cell lymphoma. J Clin Pathol. 1991;44(1):39-44.
37. Gill H, Chim CS, Au WY, Loong F, Tse E, Leung AY, et al. Non-gastric marginal zone B cell lymphoma: clinicopathologic features and treatment results. Ann Hematol. 2011;90(12):1399-407.
38. Boveri E, Arcaini L, Merli M, Passamonti F, Rizzi S, Vanelli L, et al. Bone marrow histology in marginal zone B-cell lymphomas: correlation with clinical parameters and flow cytometry in 120 patients. Ann Oncol. 2009;20(1):129-36.
39. Weiler-Sagie M, Bushelev O, Epelbaum R, Dann EJ, Haim N, Avivi I, et al. (18)F-FDG avidity in lymphoma readdressed: a study of 766 patients. J Nucl Med. 2010;51(1):25-30.
40. Hoffmann M, Kletter K, Becherer A, Jager U, Chott A, Raderer M. 18F-fluorodeoxyglucose positron emission tomography (18F-FDG-PET) for staging and follow-up of marginal zone B-cell lymphoma. Oncology. 2003;64(4):336-40.
41. van Krieken JH, Lennert K. Proliferation of marginal zone cells mimicking malignant lymphoma. Pathol Res Pract. 1990;186(3):397-9; discussion 400-2.
42. Küppers R, Hajadi M, Plank L, Rajewsky K, Hansmann ML. Molecular Ig gene analysis reveals that monocytoid B cell lymphoma is a malignancy of mature B cells carrying somatically mutated V region genes and suggests that rearrangement of the kappa-deleting element (resulting in deletion of the Ig kappa enhancers) abolishes somatic hypermutation in the human. Eur J Immunol. 1996;26(8):1794-800.
43. Chu YW, Marin E, Fuleihan R, Ramesh N, Rosen FS, Geha RS, et al. Somatic mutation of human immunoglobulin V genes in the X-linked HyperIgM syndrome. J Clin Invest. 1995;95(3):1389-93.
44. Weller S, Faili A, Garcia C, Braun MC, Le Deist FF, de Saint Basile GG, et al. CD40-CD40L independent Ig gene hypermutation suggests a second B cell diversification pathway in humans. Proc Natl Acad Sci USA. 2001;98(3):1166-70.
45. William J, Euler C, Christensen S, Shlomchik MJ. Evolution of autoantibody responses via somatic hypermutation outside of germinal centers. Science. 2002;297(5589):2066-70.
46. Berkowska MA, Driessen GJ, Bikos V, Grosserichter-Wagener C, Stamatopoulos K, Cerutti A, et al. Human memory B cells originate from three distinct germinal center-dependent and -independent maturation pathways. Blood. 2011;118(8):2150-8.
47. Warsame A, Delabie J, Malecka A, Wang J, Trøen G, Tierens A. Monocytoid B cells: an enigmatic B cell subset showing evidence of extrafollicular immunoglobulin gene somatic hypermutation. Scand J Immunol. 2012;75(5):500-9.
48. Salama ME, Lossos IS, Warnke RA, Natkunam Y. Immunoarchitectural patterns in nodal marginal zone B-cell lymphoma: a study of 51 cases. Am J Clin Pathol. 2009;132(1):39-49.
49. Jaffe ES. Nodal Marginal Zone Lymphoma. In: Jaffe ES, Harris NL, Vardiman JW, Campo E, Arber DA, eds. Hematopathology. Philadelphia: Elsevier Saunders, 2011.
50. Davis GG, York JC, Glick AD, McCurley TL, Collins RD, Cousar JB. Plasmacytic differentiation in parafollicular (monocytoid) B-cell lymphoma. A study of 12 cases. Am J Surg Pathol. 1992;16(11):1066-74.
51. Takahashi T, Suzukawa M, Akiyama M, Hatao K. Auer rod-like cytoplasmic inclusion bodies in nodal marginal zone lymphoma cells. Int J Hematol. 2009;89(2):133-4.
52. Campo E, Miquel R, Krenacs L, Sorbara L, Raffeld M, Jaffe ES. Primary nodal marginal zone lymphomas of splenic and MALT type. Am J Surg Pathol. 1999;23(1):59-68.
53. Nathwani BN, Drachenberg MR, Hernandez AM. Primary nodal marginal zone lymphomas of splenic and MALT type. Am J Surg Pathol. 2000;24(2):317-9.
54. Naresh KN. Nodal marginal zone B-cell lymphoma with prominent follicular colonization - difficulties in diagnosis: a study of 15 cases. Histopathology. 2008;52(3):331-9.
55. Siddiqi IN, Brynes RK, Wang E. B-cell lymphoma with hyaline vascular Castleman disease-like features: a clinicopathologic study. Am J Clin Pathol. 2011;135(6):901-14.
56. Pang CS, Grier DD, Beaty MW. Concomitant occurrence of sinus histiocytosis with massive lymphadenopathy and nodal marginal zone lymphoma. Arch Pathol Lab Med. 2011;135(3):390-3.
57. Ratnarathorn M, Newman J. Subcorneal pustular dermatosis (Sneddon-Wilkinson disease) occurring in association with nodal marginal zone lymphoma: a case report. Dermatol Online J. 2008;14(8):6.
58. Yoon TY, Kim YG, Kim JW, Kim MK. Nodal marginal zone lymphoma in association with hydroa vacciniforme-like papulovesicular eruption, hypersensitivity to mosquito bites and insect bite-like reaction. Br J Dermatol. 2005;153(1):210-2.
59. Went P, Ascani S, Strom E, Brorson SH, Musso M, Zinzani PL, et al. Nodal marginal-zone lymphoma associated with monoclonal light-chain and heavy-chain deposition disease. Lancet Oncol. 2004;5(6):381-3.
60. Abdou A, Asaad N. Nodal marginal zone lymphoma associated with extensive epithelioid histiocytes. Rom J Morphol Embryol. 2012;53(2):417-20.
61. Kent SA, Variakojis D, Peterson LC. Comparative study of marginal zone lymphoma involving bone marrow. Am J Clin Pathol. 2002;117(5):698-708.
62. Nathwani BN, Drachenberg MR, Hernandez AM, Levine AM, Sheibani K. Nodal monocytoid B-cell lymphoma (nodal marginal-zone B-cell lymphoma). Semin Hematol. 1999;36(2):128-38.
63. Traverse-Glehen A, Bertoni F, Thieblemont C, Zucca E, Coiffier B, Berger F, et al. Nodal marginal zone B-cell lymphoma: a diagnostic and therapeutic dilemma. Oncology (Williston Park). 2012;26(1):92-9, 103-4.
64. Molina TJ, Lin P, Swerdlow SH, Cook JR. Marginal zone lymphomas with plasmacytic differentiation and related disorders. Am J Clin Pathol. 2011;136(2):211-25.
65. Kaur P. Nodal marginal zone lymphoma with increased large cells: myth versus entity. Arch Pathol Lab Med. 2011;135(8):964-6.
66. Lennert K. Histopathologie der Non-Hodgkin Lymphome. Berlin Heidelberg: Springer-Verlag; 1981.
67. Wang E, West D, Kulbacki E. An unusual nodal marginal zone lymphoma with bright CD10 expression: a potential diagnostic pitfall. Am J Hematol. 2010;85(7):546-8.
68. Ballesteros E, Osborne BM, Matsushima AY. CD5+ low-grade marginal zone B-cell lymphomas with localized presentation. Am J Surg Pathol. 1998;22(2):201-7.
69. Camacho FI, García JF, Sánchez-Verde L, Sáez AI, Sánchez-Beato M, Mollejo M, et al. Unique phenotypic profile of monocytoid B cells: differences in comparison with the phenotypic profile observed in marginal zone B cells and so-called monocytoid B cell lymphoma. Am J Pathol. 2001;158(4):1363-9.
70. Dunphy CH. Reaction patterns of TRAP and DBA.44 in hairy cell leukemia, hairy cell variant, and nodal and extranodal marginal zone B-cell lymphomas. Appl Immunohistochem Mol Morphol. 2008;16(2):135-9.
71. Natkunam Y, Zhao S, Mason DY, Chen J, Taidi B, Jones M, et al. The oncoprotein LMO2 is expressed in normal germinal-center B cells and in human B-cell lymphomas. Blood. 2007;109(4):1636-42.
72. Miranda RN, Briggs RC, Shults K, Kinney MC, Jensen RA, Cousar JB. Immunocytochemical analysis of MNDA in tissue sections and sorted normal bone marrow cells documents expression only in maturing normal and neoplastic myelomonocytic cells and a subset of normal and neoplastic B lymphocytes. Hum Pathol. 1999;30(9):1040-9.
73. Kanellis G, Roncador G, Arribas A, Mollejo M, Montes-Moreno S, Maestre L, et al. Identification of MNDA as a new marker for nodal marginal zone lymphoma. Leukemia. 2009;23(10):1847-57.
74. Falini B, Tiacci E, Pucciarini A, Bigerna B, Kurth J, Hatzivassiliou G, et al. Expression of the IRTA1 receptor identifies intraepithelial and subepithelial marginal zone B cells of the mucosa-associated lymphoid tissue (MALT). Blood. 2003;102(10):3684-92.
75. Falini B, Agostinelli C, Bigerna B, Pucciarini A, Pacini R, Tabarrini A, et al. IRTA1 is selectively expressed in nodal and extranodal marginal zone lymphomas. Histopathology. 2012;61(5):930-41.
76. Slovak ML, Weiss LM, Nathwani BN, Bernstein L, Levine AM. Cytogenetic studies of composite lymphomas: monocytoid B-cell lymphoma and other B-cell non-Hodgkin's lymphomas. Hum Pathol. 1993;24(10):1086-94.
77. Dierlamm J, Rosenberg C, Stul M, Pittaluga S, Wlodarska I, Michaux L, et al. Characteristic pattern of chromosomal gains and losses in marginal zone B cell lymphoma detected by comparative genomic hybridization. Leukemia. 1997;11(5):747-58.
78. Dierlamm J, Michaux L, Wlodarska I, Pittaluga S, Zeller W, Stul M, et al. Trisomy 3 in marginal zone B-cell lymphoma: a

study based on cytogenetic analysis and fluorescence in situ hybridization. Br J Haematol. 1996;93(1):242-9.
79. Kim WS, Honma K, Karnan S, Tagawa H, Kim YD, Oh YL, et al. Genome-wide array-based comparative genomic hybridization of ocular marginal zone B cell lymphoma: comparison with pulmonary and nodal marginal zone B cell lymphoma. Genes Chromosomes Cancer. 2007;46(8):776-83.
80. Ferreira BI, Garcia JF, Suela J, Mollejo M, Camacho FI, Carro A, et al. Comparative genome profiling across subtypes of low-grade B-cell lymphoma identifies type-specific and common aberrations that target genes with a role in B-cell neoplasia. Haematologica. 2008;93(5):670-9.
81. Rinaldi A, Mian M, Chigrinova E, Arcaini L, Bhagat G, Novak U, et al. Genome-wide DNA profiling of marginal zone lymphomas identifies subtype-specific lesions with an impact on the clinical outcome. Blood. 2011;117(5):1595-604.
82. Baens M, Finalet Ferreiro J, Tousseyn T, Urbankova H, Michaux L, de Leval L, et al. t(X;14)(p11.4;q32.33) is recurrent in marginal zone lymphoma and up-regulates GPR34. Haematologica. 2012;97(2):184-8.
83. Braggio E, Dogan A, Keats JJ, Chng WJ, Huang G, Matthews JM, et al. Genomic analysis of marginal zone and lymphoplasmacytic lymphomas identified common and disease-specific abnormalities. Mod Pathol. 2012;25(5):651-60.
84. Brynes RK, Almaguer PD, Leathery KE, McCourty A, Arber DA, Medeiros LJ, et al. Numerical cytogenetic abnormalities of chromosomes 3, 7, and 12 in marginal zone B-cell lymphomas. Mod Pathol. 1996;9(10):995-1000.
85. Stary S, Vinatzer U, Mullauer L, Raderer M, Birner P, Streubel B. t(11;14)(q23;q32) involving IGH and DDX6 in nodal marginal zone lymphoma. Genes Chromosomes Cancer. 2013;52(1):33-43.
86. Aamot HV, Micci F, Holte H, Delabie J, Heim S. G-banding and molecular cytogenetic analyses of marginal zone lymphoma. Br J Haematol. 2005;130(6):890-901.
87. Remstein ED, James CD, Kurtin PJ. Incidence and subtype specificity of API2-MALT1 fusion translocations in extranodal, nodal, and splenic marginal zone lymphomas. Am J Pathol. 2000;156(4):1183-8.
88. Streubel B, Lamprecht A, Dierlamm J, Cerroni L, Stolte M, Ott G, et al. T(14;18)(q32;q21) involving IGH and MALT1 is a frequent chromosomal aberration in MALT lymphoma. Blood. 2003;101(6):2335-9.
89. Streubel B, Vinatzer U, Lamprecht A, Raderer M, Chott A. T(3;14)(p14.1;q32) involving IGH and FOXP1 is a novel recurrent chromosomal aberration in MALT lymphoma. Leukemia. 2005;19(4):652-8.
90. Arribas AJ, Campos-Martin Y, Gomez-Abad C, Algara P, Sanchez-Beato M, Rodriguez-Pinilla MS, et al. Nodal marginal zone lymphoma: gene expression and miRNA profiling identify diagnostic markers and potential therapeutic targets. Blood. 2012;119(3):e9-e21.
91. Novak AJ, Darce JR, Arendt BK, Harder B, Henderson K, Kindsvogel W, et al. Expression of BCMA, TACI, and BAFF-R in multiple myeloma: a mechanism for growth and survival. Blood. 2004;103(2):689-94.
92. Kojima M, Nakamura S, Itoh H, Yoshida K, Shimizu K, Motoori T, et al. Occurrence of monocytoid B-cells in reactive lymph node lesions. Pathol Res Pract. 1998;194(8):559-65.
93. Langerak AW, Molina TJ, Lavender FL, Pearson D, Flohr T, Sambade C, et al. Polymerase chain reaction-based clonality testing in tissue samples with reactive lymphoproliferations: usefulness and pitfalls. A report of the BIOMED-2 Concerted Action BMH4-CT98-3936. Leukemia. 2007;21(2):222-9.
94. Donate C, Ody C, McKee T, Ruault-Jungblut S, Fischer N, Ropraz P, et al. Homing of Human B Cells to Lymphoid Organs and B-Cell Lymphoma Engraftment Are Controlled by Cell Adhesion Molecule JAM-C. Cancer Res. 2013;73(2):640-51.
95. Gachard N, Parrens M, Soubeyran I, Petit B, Marfak A, Rizzo D, et al. IGHV gene features and MYD88 L265P mutation separate the three marginal zone lymphoma entities and Waldenstrom macroglobulinemia/lymphoplasmacytic lymphomas. Leukemia. 2013;27(1):183-9.
96. Taddesse-Heath L, Pittaluga S, Sorbara L, Bussey M, Raffeld M, Jaffe ES. Marginal zone B-cell lymphoma in children and young adults. Am J Surg Pathol. 2003;27(4):522-31.
97. Gitelson E, Al-Saleem T, Robu V, Millenson MM, Smith MR. Pediatric nodal marginal zone lymphoma may develop in the adult population. Leuk Lymphoma. 2010;51(1):89-94.
98. Rizzo KA, Streubel B, Pittaluga S, Chott A, Xi L, Raffeld M, et al. Marginal zone lymphomas in children and the young adult population; characterization of genetic aberrations by FISH and RT-PCR. Mod Pathol. 2010;23(6):866-73.
99. Kahl B, Yang D. Marginal zone lymphomas: management of nodal, splenic, and MALT NHL. Hematology Am Soc Hematol Educ Program. 2008:359-64.
100. Brown JR, Friedberg JW, Feng Y, Scofield S, Phillips K, Dal Cin P, et al. A phase 2 study of concurrent fludarabine and rituximab for the treatment of marginal zone lymphomas. Br J Haematol. 2009;145(6):741-8.