Immunoarchitectural Patterns in Nodal Marginal Zone B-Cell Lymphoma

A Study of 51 Cases

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Key Words: Nodal marginal zone lymphoma; Monocytoid B cells; Low-grade B-cell lymphoma; Immunoarchitecture; Immunohistochemistry

Abstract

Nodal marginal zone lymphoma (NMZL) represents a rare and heterogeneous group that lacks markers specific for the diagnosis. We evaluated morphologic and immunoarchitectural features of 51 NMZLs, and the following immunostains were performed: CD20, CD21, CD23, CD5, CD3, CD43, CD10, Ki-67, BCL1, BCL2, BCL6, HGAL, and LMO2. Four immunoarchitectural patterns were evident: diffuse (38 [75%]), well-formed nodular/follicular (5 [10%]), interfollicular (7 [14%]), and perifollicular (1 [2%]). Additional features included a monocytoid component (36 [71%]), admixed large cells (20 [39%]), plasma cells (24 [47%]), compartmentalizing stromal sclerosis (13 [25%]), and prominent blood vessel sclerosis (10 [20%]). CD21 highlighted disrupted follicular dendritic cell meshwork in 35 (71%) of 49 cases, and CD43 coexpression was present in 10 (24%) of 42 cases. A panel of germinal center–associated markers was helpful in eliminating cases of diffuse follicle center lymphoma. Our results highlight the histologic and immunoarchitectural spectrum of NMZL and the usefulness of immunohistochemical analysis for CD43, CD23, CD21, BCL6, HGAL, and LMO2 in the diagnosis of NMZL.

Nodal marginal zone lymphoma (NMZL) was initially described by Sheibani and colleagues in 1986 as monocytoid B-cell lymphoma because of the similarity of the neoplastic cells to monocytoid B cells that are typically seen in Toxoplasma lymphadenitis. Cousar and colleagues2 used the term parafollicular lymphoma to best illustrate the distribution of the neoplastic cells around hyperplastic follicles. Shortly thereafter, Piris and colleagues3 recognized that lymphomas arising from monocytoid B cells shared similarities with marginal zone cells based on the presence of distinctive nodal architectural and cytologic features, expression of IgM, and electron microscopic observations of short cellular processes and moderately well-developed endoplasmic reticula.

The revised European-American Classification of Lymphoid Neoplasms and the World Health Organization (WHO) classification of hematological malignancies (2001 and 2008) recognized and classified this entity as NMZL.4-6 The term NMZL is used to define marginal zone lymphomas (MZLs) with primary presentation in the lymph node in the absence of clinical evidence of prior or concurrent involvement of extranodal sites (other than the bone marrow) or spleen.7 Although the relationship among nodal, splenic, and extranodal manifestations of MZL remains controversial, multiple studies report differences in disease distribution and clinical outcome among these entities that argue for consideration of NMZL as a distinct entity,8-12 and it is therefore recognized as such in the current WHO classification.6

NMZL is an uncommon form of lymphoma representing 1.5% to 1.8% of lymphoid neoplasms,9,10 with only rare reports in the literature that have attempted morphologic or immunophenotypic characterization. Typically, NMZL has been recognized to exhibit two morphologic patterns, one resembling...
noddal involvement by extranodal MZL of mucosa-associated lymphoid tissue (MALT) and the other resembling splenic MZL. The resemblance of subsets of primary NMZL to extranodal and splenic MZLs has led to the proposal of subdividing NMZL into MALT-type and splenic-type NMZL. In addition, highly variable plasma cell, monocytoid B-cell, and large cell components, as well as follicular colonization, are also described. The lack of definitive immunophenotypic or molecular markers that are specific to this lymphoma offers a continuing challenge for diagnostic accuracy and reproducibility. We undertook this study to better characterize the morphologic and immunoarchitectural features of NMZL to enable separation of typical and variant patterns of NMZL from the other categories of low-grade B-cell lymphomas with which they overlap.

**Materials and Methods**

**Case Selection**

We conducted a retrospective review of cases between 1995 and 2004 from the archives of the Department of Pathology, Stanford University Medical Center, Stanford, CA. Institutional review board approval was obtained for these studies. Cases were selected based on the inclusion criteria of MZL with primary presentation in lymph nodes without extranodal or splenic involvement before or at the time of presentation. Extranodal and splenic MZLs were excluded by these clinical features. Although separating NMZL with clonal plasma cells from lymphoplasmacytic lymphoma (LPL) involving lymph nodes is a problem area and there are no unambiguous criteria for this distinction, cases with a significant monoclonal plasma cell component, a high degree of bone marrow involvement by a lymphoplasmacytic component, or clinical findings suggestive of LPL or plasma cell myeloma were excluded from the study.

We identified 53 cases with primary nodal presentation; 2 of these cases were eliminated after additional studies with germinal center–associated markers were performed and found to be positive. These 2 cases represented follicular lymphomas and were excluded on the basis of immunophenotypic criteria. The remaining 51 cases comprise the study population. The patients ranged in age from 19 to 87 years with a male/female ratio of 2:3. The disease in 1 patient had progressed to diffuse large B-cell lymphoma (DLBCL) as shown on a repeated biopsy 14 months after the initial diagnosis. The vast majority of cases were seen in consultation, and further clinical follow-up was not pursued because clinicopathologic correlation was not the main intent of this study.

**Morphologic Evaluation**

Morphologic evaluation was performed on formalin-fixed, paraffin-embedded tissue sections from the original diagnostic biopsies of each patient. The overall architecture together with the presence or absence of monocytoid and plasmacytoid cells and a large cell component and characteristics of stromal elements, sclerosis, and vasculature were evaluated. Follicular colonization was defined as reactive follicles that are wholly or partially overrun and virtually replaced by the neoplastic infiltrate, resulting in poorly defined follicles within which fragmented residual germinal center cells and small, darkly stained mantle zone cells are dispersed. In some cases, follicles are expanded by the infiltrating cells with loss of the characteristic zoning pattern of reactive follicles. Cells were defined as large cells if they demonstrated the following features that are characteristic of transformed B cells: enlarged nuclei (at least 2 to 3 times larger than those of small lymphocytes), open chromatin, 1 or 2 prominent nucleoli, and abundant pale cytoplasm. The presence of a large cell component was assessed by using a semiquantitative scale based on the percentage of large cells in 10 high-power fields and was categorized in the following groups: 0% to 10%, 11% to 20%, 21% to 40%, 41% to 50%, and more than 50%. In the evaluation of large cells, colonized or overrun follicles were carefully avoided with the use of antibody stains.

**Immunohistologic Studies**

For the study, 4-µm sections from representative paraffin blocks were deparaffinized in xylene and absolute ethanol and then rehydrated by successive immersions in 95% ethanol, 70% ethanol, and distilled water. All immunohistologic staining was performed on a Ventana ES instrument (Ventana Medical Systems, Tucson, AZ) using an indirect biotin–streptavidin method according to manufacturer recommendations with appropriately staining positive and negative control samples. Primary antibodies to lymphocyte markers, including CD20, CD3, CD5, CD43, BCL2, BCL1, CD21, CD23, Ki-67, CD10, BCL6, HGAL, LMO2, LMP2, LMP1, CD138, and κ and λ light chains, were applied, and a detection system using 3,3′-diaminobenzidine was used. Slides were counterstained with hematoxylin. Conditions used for immunohistochemical analysis, dilutions, and sources of all primary antibodies used in this study are shown in Table 1.

**Results**

**Architectural Patterns**

Four architectural patterns were apparent on histologic sections and have been designated diffuse, nodular/follicular, interfollicular, and perifollicular Image I. The frequency of these patterns and associated cytologic features are shown in Table 2.

The diffuse pattern, characterized by sheets of neoplastic cells with effacement of nodal architecture, represented the...
most common pattern and was evident in 38 of 51 cases. Of the cases with diffuse patterns, 18 also exhibited a vague nodular pattern as a minor component (range, 10%-40% of total area of the node evaluated). The diffuse pattern was intermixed with the nodular pattern in 1 case and the perifollicular pattern in 1 case; both patterns occupied approximately 50% of the node.

The nodular/follicular pattern was noted in 5 cases and was characterized by well-formed nodules that were well demarcated from the uninvolved interfollicular areas and replaced the normal nodal parenchyma. These nodules were crowded, monotonous in size and shape, and composed mostly of small neoplastic cells without evidence of germinal centers or a biphasic pattern (ie, inner darker and outer lighter areas such as seen in the reverse biphasic pattern in splenic MZL).

The neoplastic cells in cases with the interfollicular pattern were limited to the interfollicular areas and spared the normal secondary follicles containing germinal centers. Among the 7 cases with the interfollicular pattern, 4 showed prominent perivascular/perisinusoidal involvement.

The perifollicular pattern was characterized by annular distribution of the neoplastic cells around uninvolved normal secondary follicles and was noted only in 1 case. This pattern was noted in a second case as a minor component intermixed with a diffuse pattern.

Increased numbers of blood vessels were evident in 37 cases (73%), with vascular wall sclerosis in 10 cases (20%). Blood vessel sclerosis (thickening of small vessel walls with sclerotic material) was closely associated with the distribution of the neoplastic cells; this was most evident in cases with a nodular/follicular pattern in which sclerosis was limited to areas with follicular colonization. Interstitial sclerosis, ranging from fine to coarse sclerotic bands, was seen in 13 cases (25%). These sclerotic bands compartmentalized small groups of neoplastic cells and were most evident in cases with a diffuse pattern: 12 cases with the diffuse pattern and 1 with the nodular/follicular pattern showed interstitial sclerotic bands. One case showed associated partial involvement by Castleman lymphadenopathy–like features along the periphery of the lymph node.

**Cytologic Features**

There was variation in the size of neoplastic cells and in the shape and size of nuclei (cellular pleomorphism). Typically, a range from small to large cells was present within the neoplastic infiltrate. Cellular polymorphism was evident in 38 (75%) of 51 cases, whereas the remaining 13 cases showed predominantly small cells with occasional, scattered, intermediate-sized cells. A large cell component was identified in the following proportion of cases: 43 cases had 0% to 20% large cells, and 8 cases had 21% to 50% large cells. None of the cases showed more than 50% large cells. A higher content of larger cells (40%-50% large cells) was evident in cases with interfollicular (2 cases) and perifollicular (1 case) patterns. In addition, none of the cases with the nodular/follicular pattern showed cellular pleomorphism or a large cell component. A monocytoid B-cell component was present in 36 (71%) of 51 cases, with the following distribution: 27 diffuse, 4 nodular/follicular, and 5 interfollicular patterns. Increased numbers of plasma cells, scattered singly and in small clusters, were present in 24 cases (47%). An overt increase in eosinophils was noted in two cases, and an increase in neutrophils in association with the tumor cells was noted in another case. One case had increased numbers of histiocytes, and its corresponding involvement of the bone marrow also showed an infiltrate with increased histiocytes. Examples of typical cytologic features are shown in Image 21.

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**Table 1**

<table>
<thead>
<tr>
<th>Antibody</th>
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<th>Pretreatment</th>
<th>Dilution</th>
<th>Manufacturer</th>
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<tr>
<td>CD20</td>
<td>L26</td>
<td>Ventana*; standard retrieval</td>
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<td>DAKO</td>
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<td>Ventana; protease retrieval</td>
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<td>DAKO; pH 9.0, pressure cooker</td>
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<td>Campo et al13</td>
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<tr>
<td>LMO2</td>
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<td>1:150</td>
<td>Isaacson and Norten14</td>
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<tr>
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<td>Ventana; standard retrieval</td>
<td>1:300</td>
<td>Serotec, Oxford, England</td>
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<tr>
<td>x</td>
<td>Rabbit polyclonal</td>
<td>Ventana; protease retrieval</td>
<td>1:2,000</td>
<td>DAKO</td>
</tr>
<tr>
<td>A</td>
<td>Rabbit polyclonal</td>
<td>Ventana; protease retrieval</td>
<td>1:4,000</td>
<td>DAKO</td>
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* Ventana Medical Systems, Tucson, AZ.

Tris, tris(hydroxymethyl)aminoethane.

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The 4 immunoarchitectural patterns of nodal marginal zone lymphoma. 

A. Diffuse pattern characterized by diffuse sheets of neoplastic cells with effacement of nodal architecture (H&E, ×200).

B. Nodular/follicular pattern characterized by distinct nodules that are well demarcated from the uninvolved interfollicular areas (H&E, ×100).

C. Interfollicular pattern characterized by neoplastic cells in the interfollicular areas that surround residual germinal centers (H&E, ×100).
Immunohistologic and Immunoarchitectural Features

The immunohistologic characteristics are summarized in Table 3. In all cases, the neoplastic cells were positive for CD20. The stain for CD138 highlighted an increase in plasma cells in 24 (47% of 51 cases), and monoclonality (7 with κ and 9 with λ light chain restriction) was confirmed by immunohistochemistry or in situ hybridization in 16 (31%) of 51 cases. CD43 coexpression was observed in 10 (24%) of 42 cases, and BCL2 was detected in 12 (43%) of 28 cases. The expression of CD43 did not correlate with any particular immunohistological pattern. The stains for CD3, CD5, cyclin D1, and IgD were negative in all cases tested. CD23 was found to highlight neoplastic cells in 1 case in which the staining was diffuse but weakly positive (row 1).

The stain for CD21 was performed in 49 cases. This stain highlighted disrupted follicular dendritic cell (FDC) meshwork in 35 cases (71%), while prominent intrafollicular nests of neoplastic cells were highlighted in 13 (27%) cases (row 2). The intrafollicular nests of neoplastic cells were found in 7 cases with a diffuse pattern, 4 with the nodular/follicular pattern, and 1 with the perifollicular pattern. Intact or disrupted FDC meshwork associated with residual germinal centers was absent in 8 cases exhibiting a diffuse pattern and in 1 with the nodular/follicular pattern. The stain for CD23 highlighted residual and disrupted FDC meshwork in 8 (40%) of 20 cases, all of which corresponded to the cases that were also highlighted by CD21 staining. The proliferation marker, Ki-67, was evaluated in 13 cases: a high growth fraction was present in residual germinal centers; the neoplastic proliferation showed a range of staining from 5% to 40%, which was primarily localized to scattered transformed large cells (row 3).

Separation of the nodular/follicular pattern of NMZL from follicular lymphoma, particularly in cases of follicular lymphoma with a diffuse component, can be problematic. The pattern of staining for CD20, BCL2, and germinal center–associated markers can aid in this separation, as shown in a typical case of NMZL with a nodular/follicular pattern and associated immunohistologic stains (row 1).

A panel of 4 germinal center–associated markers, CD10, BCL6, HGAL, and LMO2, was used to eliminate cases of diffuse follicle center lymphoma that show morphologic overlap with NMZL. Initially, 53 cases were retrieved from

Table 2
Architectural Patterns and Associated Cytologic Features in Nodal Marginal Zone B-Cell Lymphoma*
our files with the diagnosis of NMZL that fulfilled criteria for this study. Staining for CD10 was uniformly absent in all 53 cases; however, 2 cases showed staining for BCL6, HGal, and LMO2 (both cases showed diffuse staining for BCL6 and LMO2; one case showed weak focal staining for HGal). This staining was convincingly localized to the neoplastic cells and was not related to residual germinal center cells in colonized or overrun follicles. The typical cell milieu in NMZL showed a range from small to medium-sized cells with clear cytoplasm (monocytoid cells) with occasional admixed large cells (D, H&E, ×500), increased large cells with nuclear pleomorphism (E, H&E, ×1,000), and plasmacytoid cells scattered singly and in clusters (F, H&E, ×400).

Discussion

Currently, the WHO guidelines for the diagnosis of lymphoid malignancies require the integration of clinical, morphologic, immunophenotypic, and genetic information for a definitive diagnosis. To date, no immunophenotypic or genetic marker specific to NMZL has been identified. Therefore, the diagnosis of this entity relies on the recognition and development of diagnostic criteria based solely on morphologic and immunoarchitectural patterns and the integration of clinical data at the time of presentation to determine a diagnosis. Because of the rarity of NMZL, large series that
thoroughly characterize their pathologic features are limited. In this study, we morphologically and immunophenotypically characterized, to the best of our knowledge, the largest series of primary NMZL cases that meet the current WHO criteria for this entity. We define 4 distinct immunoarchitectural patterns of NMZL that we have designated diffuse, nodular/ follicular, interfollicular, and perifollicular and describe their histologic and immunoarchitectural features.

Peripheral lymph node involvement can be seen in extranodal and splenic MZLs.\textsuperscript{9,17} Thus, in our cohort, we excluded any case with extranodal disease, splenic, or splenic hilar lymph node involvement. The distinction between NMZL with clonal plasma cells and LPL involving lymph nodes is problematic, and currently there are no unequivocal criteria to separate these entities. As such, the morphologic and immunoarchitectural features need to be assessed in the light of clinical manifestations. In the current study, we excluded cases with an increased monoclonal plasma cell component in the lymph node, extensive marrow involvement, and clinical or radiologic features suggestive of LPL or plasma cell myeloma. Although plasma cells were noted in a large proportion of our cases (47%), they represented only a minor component of the neoplastic infiltrate in the lymph node. All cases described in this report met strict diagnostic criteria for NMZL with primary lymph node presentation and absence of extranodal or splenic disease at the time of this study. It is, however, important to consider that some cases of NMZL may manifest as extranodal disease on follow-up and represent secondary involvement of lymph nodes.\textsuperscript{13}

In accord with previous studies, diffuse effacement of architecture (the diffuse pattern) was most commonly encountered with an associated vague nodular pattern in 47% of cases. In cases with both patterns, the diffuse pattern usually represented the major component, and the nodular pattern was a minor component occupying approximately 10% to 40% of the lesion. Traverse-Glehen and colleagues\textsuperscript{18} made a similar observation that cases with the diffuse pattern are closely associated with a nodular pattern. In contrast with the findings of previous studies,\textsuperscript{10,18} we identified well-formed follicles in 10% of cases but did not observe any with the so-called inverse follicular pattern. This inverse follicular pattern, which has been described as a follicle with a dark-staining inner zone surrounded by a light-staining outer zone on H&E sections, is typically seen in a subset of splenic MZL and a small number of NMZL (2 of 21) cases in an earlier study.\textsuperscript{18}

A problematic area in the diagnosis of NMZL with a well-defined follicular/nodular or diffuse pattern is its separation from low-grade follicular lymphoma. Germinal center–associated markers that highlight follicular lymphoma cells are typically absent in NMZL. However, subsets of follicular lymphoma may also lack germinal center–associated markers, making the distinction between these entities a diagnostic challenge. We encountered 2 such cases with a diffuse pattern that were originally diagnosed as NMZL based on the lack of CD10 staining. However, with the use of additional germinal center–associated markers, these cases were reclassified as diffuse follicle center lymphomas. In this context, BCL6, HGAL, and LMO2 performed better than did CD10 and showed more sensitivity and specificity for follicular lymphoma cells. In these 2 cases, CD21 immunostaining highlighted disrupted FDC meshwork, a finding that further confounded their separation from NMZL. Overall, CD21 highlighted disrupted FDC meshwork with follicular colonization in the majority of cases in our cohort (71%), regardless of the morphologic pattern, although it was more prominent in cases with a well-defined follicular/nodular pattern (4/5 [80%]). In a recent study of 15 NMZLs with prominent follicular colonization, the difficulty in distinguishing NMZL from other low-grade lymphomas with a follicular pattern is well illustrated.\textsuperscript{19} Our findings are in agreement with that study and further highlight the need for recognition of the extensive disruption of FDC meshwork and follicular colonization that is often seen in NMZL.

The presence of follicular colonization and disrupted FDCs in some cases and the complete absence of FDCs in other cases suggest a possible evolution of tumor pattern in NMZL. The cases that showed a complete absence of FDCs likely represent more advanced tumors that replace the lymph node architecture. We were unable to verify whether the attrition and eventual absence of FDC meshwork correlate with progression of disease in our cohort of cases because clinical follow-up information was limited. However, this concept warrants further examination on clinically well-characterized cases.

### Table 3

<table>
<thead>
<tr>
<th>Antibody</th>
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<tr>
<td>CD20</td>
<td>51/51 (100)</td>
</tr>
<tr>
<td>CD3 or CD5</td>
<td>0/51 (0)</td>
</tr>
<tr>
<td>CD43</td>
<td>10/42 (24)</td>
</tr>
<tr>
<td>BCL2</td>
<td>12/28 (43)</td>
</tr>
<tr>
<td>BCL1</td>
<td>0/13 (0)</td>
</tr>
<tr>
<td>IgD</td>
<td>0/26 (0)</td>
</tr>
<tr>
<td>CD21</td>
<td>0/49 (0; lymphoma cells)</td>
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<td>Follicular colonization</td>
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<td>Disrupted FDC meshwork</td>
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<td>Monoclonal plasma cells</td>
<td>16/51 (31)</td>
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FDC, follicular dendritic cell.
Immunohistologic staining for CD43 and BCL2 can be helpful in the diagnosis of NMZL but shows significant variation among cases and in rates of positivity reported in previously published studies. Staining for CD43 is reported to range from 20% to 75%, whereas the staining for BCL2 has been reported to range from 62% to 100%. Lai and colleagues showed that CD43 staining was positive in 20% to 40% of nodal and extranodal MZLs, and staining for CD43 in our cohort was in the same range. However, BCL2 positivity was significantly lower in our cohort. A number of factors may be responsible for this difference, including differences in methods and antigen retrieval among cases sent in consultation. In addition, the inclusion criteria used in some studies whereby cases were selected based on their positivity of CD43 and/or BCL2 may also play into the higher number of positive cases reported in published series. Nevertheless, it is important to recognize that although immunohistologic stains for CD43 and BCL2 are helpful when present and aid in identifying the neoplastic B-cell infiltrates on which they are coexpressed, their expression is not essential for the diagnosis of NMZL. In addition, other B-cell non-Hodgkin lymphomas such as mantle cell lymphoma (frequently positive for CD43 and BCL2) and follicular lymphoma (particularly, diffuse follicle center lymphoma) should also be carefully eliminated from the differential diagnosis.

Another important morphologic consideration in the diagnosis of NMZL is its relationship to DLBCL, which is particularly problematic in NMZL with increased large
This finding of increased scattered large cells should not be confused with sheets of large cells, particularly if the latter is associated with an increase in proliferation (as measured by Ki-67 staining), because sheets of large cells, even if focal, should raise concern for progression to large cell lymphoma.

Kojima and colleagues recently reported a series of 65 cases of NMZL, of which 20 cases had more than 50% large cells or sheets of large cells and were classified as “DLBCL + MALT-type NMZL”; these cases were associated with a significantly worse outcome. Our cohort did not include cases with more than 50% large cells or sheets of large cells and, thus, met

transformed B cells. Nathwani and colleagues described progression to DLBCL as the cases with more than 20% large cells. In our cohort, however, we found more than 20% large cells in 16% of cases: many of these cases exhibited increased numbers of scattered large cells, and in a minority of cases, up to 50% of large cells were present. These cases showed no significant correlation with a particular morphologic pattern and did not correspond to the 1 case that showed transformation to large cell lymphoma in a subsequent biopsy.

In addition, none of our cases demonstrated sheets of large cells. Similar to the findings of Traverse-Glehen et al., our findings suggest that the presence of a large cell component in NMZL is more frequent than previously recognized. The finding of increased scattered large cells should not be confused with sheets of large cells, particularly if the latter is associated with an increase in proliferation (as measured by Ki-67 staining), because sheets of large cells, even if focal, should raise concern for progression to large cell lymphoma. Kojima and colleagues recently reported a series of 65 cases of NMZL, of which 20 cases had more than 50% large cells or sheets of large cells and were classified as “DLBCL + MALT-type NMZL”; these cases were associated with a significantly worse outcome. Our cohort did not include cases with more than 50% large cells or sheets of large cells and, thus, met...
particularly challenging. In our experience, the use of additional germinal center–associated markers is helpful in ruling out follicular lymphoma, particularly if staining for CD10, a marker frequently used in immunohistologic panels, is absent. In this study, we found that together with BCL6, HGAL and LMO2, 2 recently characterized germinal center B cell–associated markers, are excellent adjuncts in the immunohistologic workup of low-grade B-cell lymphomas, especially those that exhibit a diffuse small lymphoid proliferation.

We describe a large series of primary NMZLs that highlights the heterogeneity of this disease and exhibits a spectrum of morphologic and immunophenotypic variability. The 4 immunoarchitectural patterns we describe, together with their frequency and potential overlap with other lymphomas in the differential diagnosis, provide a greater understanding of the inherent heterogeneity of this lymphoma. The presence of large cells in a significant proportion of cases and the inclusion of germinal center–associated markers in their workup support and extend previous observations. In addition, we found that CD21 staining was particularly useful in highlighting disrupted FDC meshwork and follicular colonization, a feature that lends support for the diagnosis of MZL. Recent gene expression profiling studies of splenic MZL have pointed to specific abnormalities in that entity, which, after
further testing and validation, can be used for the diagnosis of splenic MZL. Similarly, genomic and proteomic approaches to interrogate NMZL will be needed and will likely furnish candidate markers specific to the diagnosis. In the interim, awareness of the immunoarchitectural patterns of NMZL is important for making an accurate and reproducible diagnosis and for distinguishing this entity from other lymphomas in the differential diagnosis.

References