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Nodal and leukemic small B-cell neoplasms

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The small B-cell neoplasms represent some of the most frequently encountered lymphoproliferative disorders in routine surgical pathology practice. This report reviews the current diagnostic criteria for classifying small B-cell neoplasms and distinguishing them from newly recognized precursor conditions that do not appear to represent overt lymphomas. Newly available immunohistochemical stains and molecular studies that may assist in the diagnosis and classification of these neoplasms are also discussed.
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The nodal and leukemic small B-cell neoplasms are a heterogeneous group of entities that represent some of the most frequent lymphoproliferative disorders seen in routine clinical practice.[1] The major entities in this category, follicular lymphoma (FL), chronic lymphocytic leukemia/small lymphocytic lymphoma (CLL/SLL), mantle cell lymphoma (MCL), nodal marginal zone lymphoma (NMZL), and lymphoplasmacytic lymphoma (LPL), are distinguished by characteristic morphological features together with characteristic phenotypic and cytogenetic findings (Table 1). With the exception of MCL, which typically displays an aggressive clinical course usually treated by multiagent chemotherapy, the small B-cell neoplasms generally have an indolent clinical course. These lymphomas are generally uncurable by current protocols and treatment is typically initiated with palliative intent; watch and wait management strategies may be used for asymptomatic patients in some cases.

The following summary is not intended to be a thorough review of the pathobiology of the small B-cell neoplasms. Rather, this paper aims to provide a summary of current diagnostic criteria for these lymphomas and to provide a brief guide for routine diagnosis and classification in routine practice. A recurring theme in the recent literature is a recognition of early lesions that challenge the current paradigm that all lymphomas should be considered malignant neoplasms.[2] Current recommendations regarding the distinction of these early lesions from overt lymphomas are discussed. In addition, recent findings regarding newer phenotypic or cytogenetic data are discussed that may assist in the diagnosis and classification of these disorders.

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Follicular lymphoma

FL is a neoplasm composed of follicle center (germinal center (GC)) B-cells (typically both centrocytes and centroblasts/large transformed cells), which usually has at least a partially follicular pattern. FL accounts for ~30% of all non-Hodgkin lymphomas in adults in Western countries, and the incidence of this disorder has been increasing over recent years.[3,4] This entity therefore represents the most commonly encountered type of small B-cell lymphoma in routine pathology practice. The median age of diagnosis is in the sixth decade, and there is a slight female predominance. Most patients (~80%) will present with advanced disease (Stage III or IV). The distribution of disease is predominantly nodal, while initial presentation as an isolated extranodal lesion is uncommon.

Morphologically, FL typically shows effacement of the lymph node architecture by a follicular or follicular and diffuse proliferation of small-cleaved cells admixed with variable numbers of centroblasts/large-transformed cells (Figure 1). The malignant GCs of FL typically show indistinct or absent mantle zones, few if any tingible body macrophages, and lack polarization (separation into dark zones and light zones). Recognition of these morphological features assists in distinguishing the malignant GCs of FL from the reactive GCs seen in follicular hyperplasia. Cases displaying centrocytes and centroblasts growing in a purely diffuse pattern are rare ('diffuse FL') and should be diagnosed as such only

Table 1 Phenotypic and genotypic markers of small B-cell neoplasms

Marker	*FL*	*CLL/SLL*	*MCL*	*NMZL*	*LPL*
CD5	−	+	+	−	−
CD10	+	−	−	−	−
BCL6	+	−	−	−	−
CD23	+/−	+	−	−/+	−/+
LMO2[a]	+	−	−	−	−
HGAL[a]	+	−	−	−	−
GCET1[a]	+	−	−	−	−
SOX11[a]	−	−	+	−	−
LEF-1[a]	−/+	+	−	−	−
IGH/BCL2	+/−	Rare	−	−	−
IGH/CCND1	−	−	+	−	−
t(*BCL6*)	−/+	−	−	−	−

Abbreviations: CLL, chronic lymphocytic leukemia; FL, follicular lymphoma; LPL, lymphoplasmacytic lymphoma; MCL, mantle cell lymphoma; NMZL, nodal marginal zone lymphoma; SLL, small lymphocytic lymphoma.
[a]Newer marker discussed in this session.

following complete phenotypic and/or cytogenetic characterization as described below.[3]

Using 2008 WHO criteria, FL are graded by the number of centroblasts per high-power field (Table 2). However, it has been shown that there is little if any biological distinction between grade 1 and grade 2 FL, and there is poor reproducibility of FL grading even among 'expert' pathologists.[3,5] The 2008 classification scheme therefore strongly recommends grouping grade 1 and 2 cases together and issuing a diagnosis of 'grade 1–2 FL'. Cases with a sufficient number of centroblasts to fulfill the criteria for a grade 3 FL are further subdivided based on the presence (grade 3A) or absence (grade 3B) of admixed centrocytes. Although somewhat controversial, this distinction is encouraged as there is evidence that grade 3B cases display unique biological features.[6,7]

The diagnosis of FL is based in part upon demonstration of a GC phenotype within the neoplastic cells. FL is typically positive for CD10 and BCL6 by immunohistochemistry, and usually positive for CD10 by flow cytometry. The demonstration of interfollicular staining for CD10 is particularly useful in establishing diagnosis. This finding is not present in all cases, however, as the interfollicular component of the tumor often downregulates expression of this antigen.[8–10] BCL6 staining is usually restricted to the follicular component, with only a minority of cases showing interfollicular BCL6-positive cells. It should be noted that a minority of cases, usually of grade 3 morphology, may lack CD10 expression entirely. These cases typically retain expression of BCL6 at least within the GCs, but create a differential diagnosis with marginal zone lymphoma. BCL2 is coexpressed by the neoplastic cells in ~85% of cases overall, with an even higher incidence observed in cases with grade1–2 morphology.[11–13]

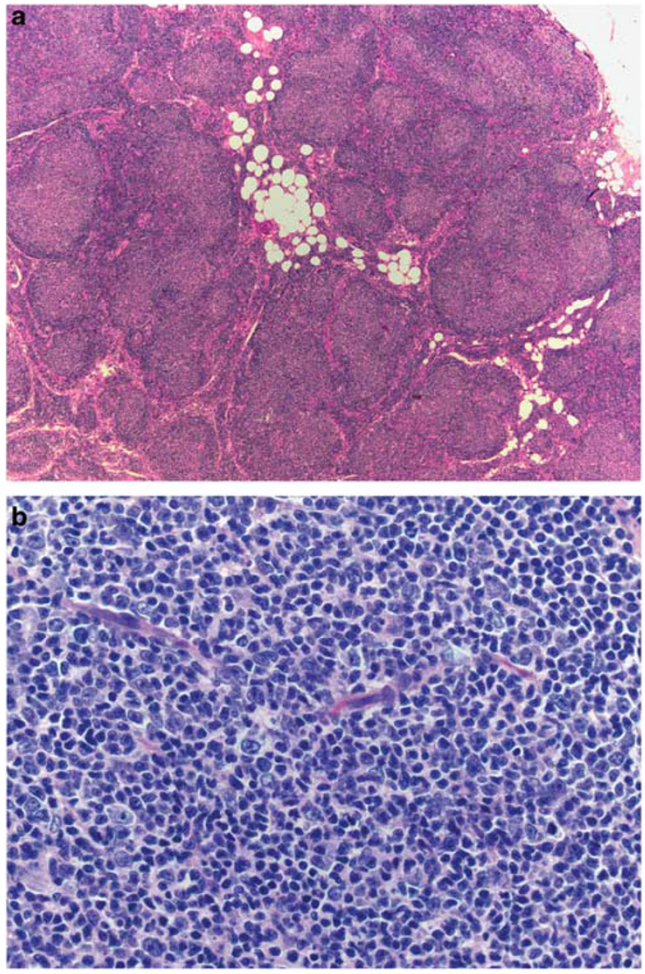

Figure 1 Morphology of FL. (**a**) At low magnification, FL displays a follicular growth pattern with numerous back-to-back GCs. (**b**) At high magnification, the lymphoma is composed of numerous centrocytes admixed with occasional centroblasts.

Table 2 Grading of follicular lymphoma

Grade	*Centroblasts*	*Other criteria*
Grade 1–2	0–15/hpf	
Grade 3A	>15/hpf	Centrocytes present
Grade 3B	>15/hpf	Centrocytes absent

Note: Grading is based on examination of 10 representative high-power field (hpf) with a hpf of 0.159 mm^2 (40 × objective, 18 mm f.o.v. ocular). For other oculars, adjustments to cutoffs are necessary.[3]

Care should also be taken to confirm that BCL2 expression is seen in GC-cells, not in primary follicles, or in secondary follicles tangentially cut such that only mantle zone cells are visible. Although the demonstration of BCL2 coexpression by malignant GCs greatly facilitates recognition of FL, absence of BCL2 expression does not exclude this diagnosis.

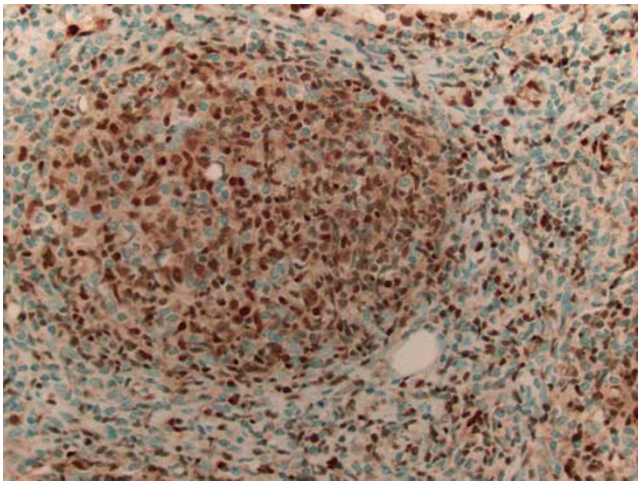

Figure 2 LMO2 expression in FL. The intrafollicular cells and a subset of the extrafollicular cells show nuclear expression of LMO2.

More recently, additional antibodies against GC antigens have become commercially available including LMO2 (Figure 2), HGAL, and GCET1. Several studies have shown that these newer markers are also positive in the majority of cases of FL (>70% for LMO2 and >90% for HGAL and GCET1)[14–17]. In routine practice, the diagnosis of FL can typically be established using CD10 and BCL6 as GC markers, but these newer GC-associated markers may also be helpful in selected cases, such as CD10-negative FL.

The cytogenetic hallmark of FL is the t(14;18)(q32;q21) *IGH*/*BCL2* translocation. This translocation leads to aberrant expression of BCL2 protein by the malignant GC cells, leading to inhibition of apoptosis and enhanced survival. This translocation is found in ~85% of FL overall, but is more common in grade 1–2 FL (~90% incidence) than in grade 3 cases (~50% incidence).[3,4,18] Because immunohistochemistry can easily demonstrate coexpression of BCL2 with either CD10 or BCL6 in the great majority of cases, molecular studies for an *IGH*/*BCL2* translocation need not be performed in most circumstances. In more challenging cases, the demonstration of an *IGH*/*BCL2* translocation in a small B-cell lymphoma is a helpful finding in support of a diagnosis of FL. It should be remembered, however, that this translocation is not unique to FL and can be seen in other lymphomas including DLBCL and, rarely, CLL/SLL.[19,20]

The t(14;18)(q32;q21) can be detected using several techniques. This translocation can be identified by standard metaphase cytogenetics, but these are often not performed on lymph node biopsies at many institutions. PCR studies are available and may be particularly helpful in detecting relatively low-level disease, such as in the bone marrow. PCR studies may show limited detection rates, however, because it is difficult to design primers capable of encompassing all of the known variations in translocation breakpoints. For this reason, fluorescence *in situ* hybridization (FISH) studies are generally preferable to PCR in routine practice for initial diagnosis.[21–23] FISH studies can be performed utilizing either dual fusion probes, which are specific for *IGH*/*BCL2*, or using *BCL2* break-apart probes, which identify any *BCL2* translocation but do not specifically identify the translocation partner gene involved.

Interestingly, studies have recently shown that up to half of cases of FL that appear to lack BCL2 protein by immunohistochemistry actually contain a t(14;18) by FISH.[24,25] In the majority of these cases, BCL2 protein is actually expressed, but mutations have accumulated within the *BCL2* gene that disrupt the binding site for the most commonly used anti-BCL2 antibodies. BCL2 expression can be confirmed in these 'BCL2 pseudo-negative' cases using other, more recently developed BCL2 antibodies.[24–26]

Translocations involving the *BCL6* gene occur in ~15% of FL, with most of these occurring in cases with grade 3 morphology in the absence of *IGH*/*BCL2* translocations.[12,18,26] *BCL6* translocations may have many different partner genes, including the *IGH* locus. *BCL6* translocations are most efficiently identified by FISH using a two-color, break apart *BCL6* probe. *BCL6* translocations, however, are not specific for FL, and can also be found in ~40% of DLBCL and occasionally in other small B-cell lymphomas.

Variant—Pediatric FL

Although occurring predominantly in older adults, FL also presents rarely in childhood. Pediatric FL cases show many features similar to those in adults, but there are several differences that have led the WHO to recognize pediatric FL as a distinct clinical variant.[3] Specifically, pediatric FL shows an increased proportion of cases with focal disease, grade 3 morphology, lack of BCL2 protein by immunohistochemistry, and lack of the *IGH*/*BCL2* translocation.[27,28] In light of these findings, it is often challenging to distinguish between florid follicular hyperplasia and pediatric FL. It should be remembered that follicular hyperplasia may sometimes yield a clonal B-cell population by PCR or even by flow cytometry.[29] Clear cut morphological evidence of lymphoma is therefore critical in establishing this diagnosis. Many cases show admixed areas of DLBCL, which may also help facilitate diagnosis. Interestingly, a coexisting DLBCL component does not appear to alter the prognosis in pediatric FL, unlike in adult cases.[27] Pediatric FL appears to show a favorable clinical course. Interestingly, a recent study has identified frequent *IRF4*/*MUM1* translocations in cases of FL and DLBCL occurring in childhood and young

adults.[30] Additional studies will be required to determine whether this abnormality may be used as a diagnostic marker for pediatric type FL.

Precursor Lesion—'FL *In Situ*'

Using very sensitive PCR techniques (much more sensitive than those typically used for diagnostic purposes), it has been shown that up to two-third of normal adults with no evidence of malignant lymphoma have detectable clonal B-cell populations that carry the t(14;18) in the peripheral blood.[31,32] This very small population of B-cells is thought to carry the t(14;18) as a 'first hit' in neoplastic development, but to lack sufficient additional abnormalities for overt malignant transformation. More recently, it has been shown that some otherwise unremarkable lymph nodes with complete architectural preservation from patients without evidence of overt lymphoma can show BCL2-positive GCs that contain clonal B-cell populations and the *IGH*/*BCL2* (Figure 3).[33–35] In some cases, only a few or even a single neoplastic GC may be present in the lymph node. These cases of so-called 'FL *in situ*' (also termed '*in situ* involvement by FL-like cells' or 'FL-like B-cells of uncertain significance') are thought to represent the tissue equivalent of the rare circulating *IGH*/*BCL2*-positive cells detectable in normal peripheral blood. A recent study examined 1294 lymph nodes from 132 consecutive patients removed for any surgical procedure, and reported FL *in situ* in ~2% of patients.[36] Because FL *in situ* appears to be more common than overt FL, it is thought that many patients with FL *in situ* will not progress to overt FL.

The emergence of the concept of FL *in situ* has shed light on the development pathways of this common type of lymphoma, but has also created several difficulties for the diagnostic surgical

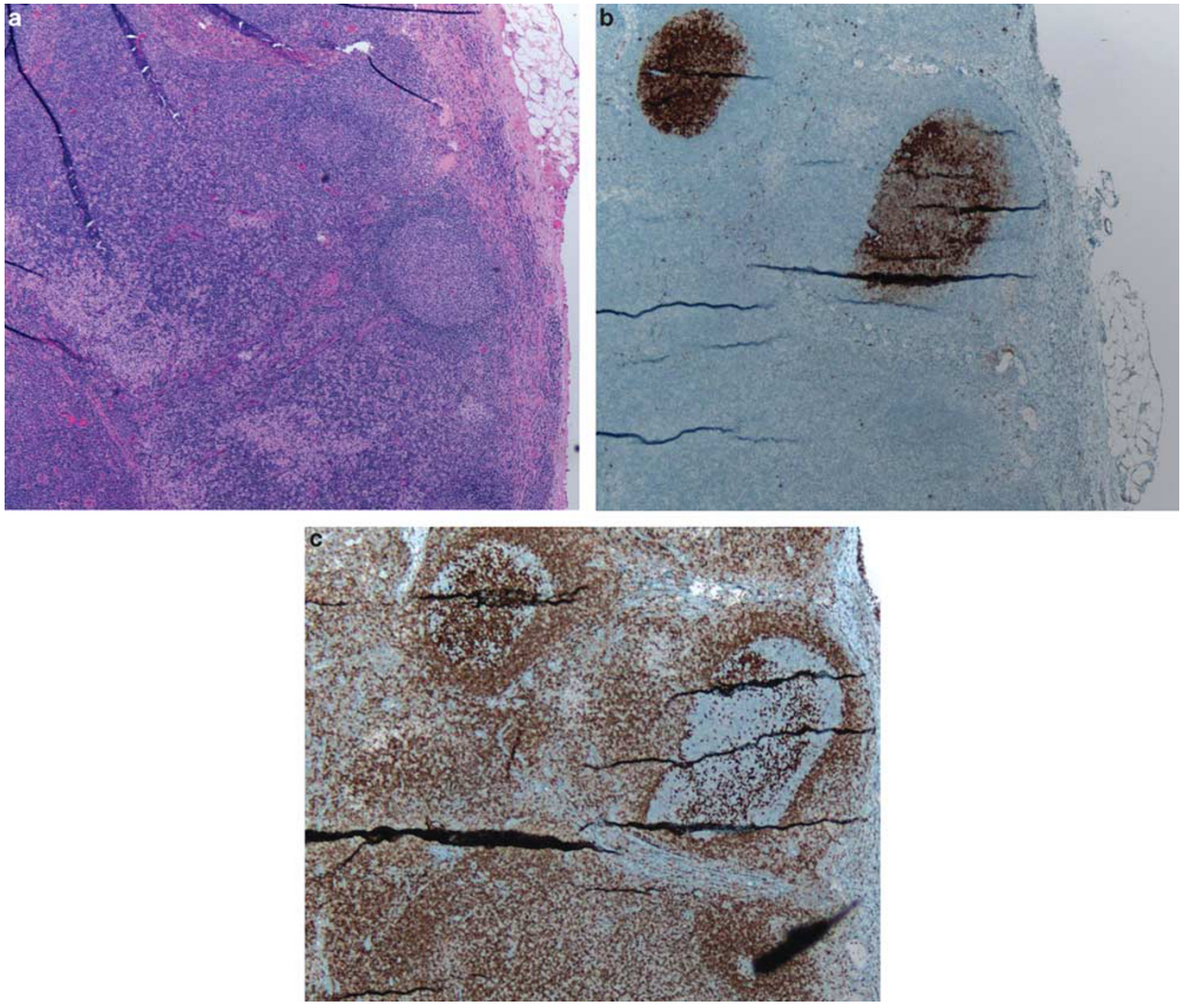

Figure 3 *In situ* FL. (**a**) At low magnification, this lymph node is essentially unremarkable. (**b**) A CD10 immunostain highlights the GCs. (**c**) A BCL2 stain shows that many of the GC cells coexpress BCL2 protein.

pathologist. First, one must distinguish between FL *in situ* and partial lymph node involvement by FL. By definition, FL *in situ* must show preserved lymph node architecture. The presence of even focal areas with back-to-back GCs, obliterated sinuses, or extra-follicular B-cells with a GC phenotype excludes this diagnosis.[34] Because some patients with FL *in situ* in one sampled lymph node may have overt FL at other sites, staging studies are appropriate. In the absence of overt clinical disease, observation alone has been strongly suggested, although formal management guidelines for this condition remain lacking.[2,34]

Chronic lymphocytic leukemia/small lymphocytic lymphoma

The WHO currently defines CLL/SLL as a neoplasm of monomorphic, small, round to irregular B-cells admixed with prolymphocytes and paraimmunoblasts, forming proliferation centers in tissue infiltrates and usually expressing CD5 and CD23.[37] The distinction between the diagnoses of CLL, SLL and the precursor condition, monoclonal B lymphocytosis is based on the presence of adenopathy and the number of peripheral blood B cells as determined by flow cytometry (Table 3). The International Workshop on Chronic Lymphocytic Leukemia (IWCLL) criteria,[38] widely used in many research protocols, further considers cytopenias due to bone marrow infiltration or other disease-related symptoms to be diagnostic of CLL regardless of peripheral blood B-cell count or adenopathy.

Clinically, CLL and SLL generally share most clinical features and are considered to represent clinical variants of the same disease with patients presenting with leukemic involvement diagnosed as CLL and patients presenting with primarily nodal involvement diagnosed as SLL.[37] CLL, the most common form of leukemia in Western countries, typically presents in adults with a mean age of 65 at first diagnosis and there is a male predominance (2:1 M:F). Many patients are asymptomatic at first presentation, with lymphocytosis noted incidentally, while others may present with anemia, thrombocytopenia, or adenopathy. Approximately 60% of patients have hypogammaglobulinemia, which predisposes to infection.[39] SLL, which accounts for only 5–10% of CLL/SLL overall, occurs in a similar demographic group and usually presents with widespread adenopathy. Most patients with SLL present at high stage due to bone marrow involvement.

In CLL, there is by definition $>5\times10^9$/l clonal B-cells in the peripheral blood detected by flow cytometry. The lymphocytes are small with coarsely clumped chromatin, round nuclear contours, and scant cytoplasm. As the neoplastic cells are more fragile than typical, benign small lymphocytes, peripheral smears often show numerous disrupted cells ('smudge cells'). In the bone marrow, infiltrates of small lymphocytes may be present interstitially, diffusely, or as nodular aggregates.

In CLL/SLL, there is effacement of the lymph node architecture by an essentially diffuse infiltrate of small lymphocytes with clumped chromatin, round nuclei, and scant cytoplasm (Figure 4).[37] Variable

Table 3 Diagnostic criteria for SLL, CLL and MBL

	Pathologic adenopathy?	*B-cells in PB*
Small lymphocytic lymphoma	Yes	$<5\times10^9$/l
Chronic lymphocytic leukemia	Yes or no	$>5\times10^9$/l
Monoclonal B lymphocytosis	No	$<5\times10^9$/l

Abbreviations: CLL, chronic lymphocytic leukemia; MBL, monoclonal B-cell lymphocytosis; SLL, small lymphocytic lymphoma.

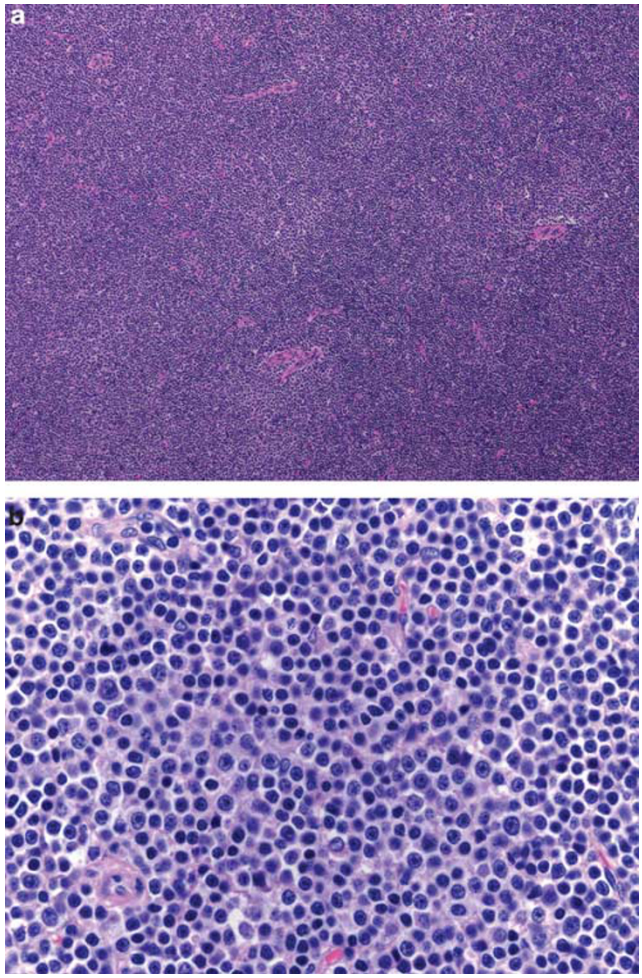

Figure 4 Morphology of CLL/SLL. (**a**) At low magnification, this lymph node contains a predominantly diffuse infiltrate with vaguely nodular paler proliferation centers. (**b**) At higher magnification, the proliferation centers contain small lymphocytes admixed with occasional prolymphocytes and paraimmunoblasts.

numbers of proliferation centers may be present. Proliferation centers are focal areas containing somewhat larger cells with more abundant cytoplasm admixed with prolymphocytes and paraimmunoblasts. In some cases, proliferation centers may become prominent and be mistakenly interpreted as GCs. The presence of increased, or even confluent proliferation centers should not be misdiagnosed as large cell transformation, although this pattern has been reported to be associated with a poor prognosis.[40] A diagnosis of transformation to DLBCL (Richter's transformation) should be made only in the presence of sheets of large transformed cells.

The neoplastic cells in CLL/SLL are positive for CD5 and CD23, and are negative for CD10, FMC7, and Cyclin D1. Surface immunoglobulin expression is typically of dim intensity. It should be noted, however, that many exceptions to this phenotypic profile occur (uncharacteristically bright surface immunoglobin, positivity for FMC7, dim to negative CD23, negative for CD5), and such cases have sometimes been referred to as 'atypical CLL'.[41–43] Recently, additional markers have also been described that may be of assistance in challenging cases. Nuclear expression of LEF-1, a mediator of the WNT/β-catenin signaling pathway, is found in $>95\%$ of cases of CLL/SLL (Figure 5), including cases lacking CD5 expression. LEF-1 staining has also been described in a subset of FL and DLBCL, but is reported to be absent in MCL.[44] Conversely, SOX11 is a nuclear transcription factor found in the vast majority of MCLs (see Mantle cell lymphoma section), but absent in CLL/SLL.[45–47] Use of these two newer markers may be very helpful to distinguish cases of CLL/SLL from MCL and other small B-cell neoplasms.

The malignant cells in CLL/SLL grow poorly in culture, and so metaphase cytogenetic analysis is usually unsuccessful. FISH studies however show that several cytogenetic abnormalities are common in CLL and can be used for prognostic assessment (Table 4).[48,49] In particular, the loss of the *TP53* locus at 17p13 is associated with lack of response to fludarabine, a commonly used agent, and unfavorable clinical course. FISH studies have therefore become routine at many institutions at first diagnosis. Although less well studied in SLL than in CLL, the same spectrum of abnormalities has also been documented to occur.[50]

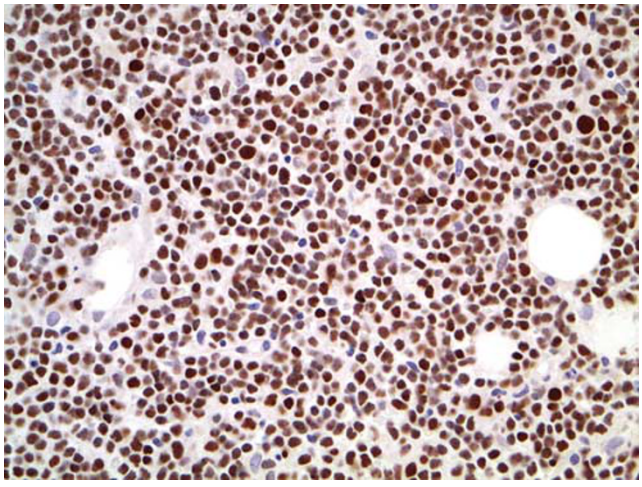

Figure 5 LEF1 expression in CLL/SLL. The B-cells in this case exhibit strong nuclear expression of LEF1.

Precursor Lesion—Monoclonal B Lymphocytosis

The increasing use of peripheral blood flow cytometric studies over the years has demonstrated that $\sim 5\%$ of adults over age 60 in the general population carry a relatively low level of clonal B cells with a phenotype identical to that seen in CLL. The IWCLL and later the WHO therefore adopted the diagnosis of monoclonal B-cell lymphocytosis (MBL) to identify these patients with $<5 \times 10^9$/l monoclonal B-cells in the peripheral blood.[37] Approximately 1–2% of MBL patients per year progress to CLL, although many MBL patients never require therapy.[51,52] It should be noted, however, that this cutoff was chosen in a rather arbitrary fashion, and recent studies have attempted to define a biological cutoff threshold based on time to first therapy requirements. These studies have generally suggested that a higher cutoff, perhaps as high as $10–11 \times 10^9$, may be more useful for the distinction between MBL and CLL.[52–54] This remains an area of controversy that will likely be addressed in future revisions of the WHO classification. In addition, there are currently no accepted criteria for distinction between MBL and CLL/SLL based on the extent of bone marrow involvement alone. Even the possibility of MBL with lymph node involvement has been raised.[55,56] For this reason, bone marrow biopsy alone cannot be used to make this distinction. When a CD5-positive B-cell disorder consistent with MBL/CLL/SLL is unexpectedly identified in a bone marrow biopsy, peripheral blood flow cytometry studies are necessary to quantify peripheral blood B cells for final classification.

Mantle cell lymphoma

The 2008 WHO classification defines MCL as a B-cell neoplasm of monomorphic small to medium sized lymphoid cells with irregular nuclear contours

Table 4 Cytogenetic abnormalities in CLL[48]

Abnormality	*Frequency (FISH)*	*Prognosis*
Del(13q)	30–50%	Favorable
+12	15–20%	Intermediate
None	20%	Intermediate
Del(11q)	15–20%	Unfavorable
Del(17p)	5–10%	Unfavorable

Abbreviation: CLL, chronic lymphocytic leukemia.

and a *CCND1* translocation. MCL presents in adulthood, with a median age in the seventh decade and with a male predominance.[57,58] Most patients present with advanced stage disease (stage III–IV) at presentation. The most common presentation consists of progressive widespread adenopathy and/or splenomegaly. In a minority of patients, the disease presents predominantly in the gastrointestinal tract with numerous sessile polyps, a presentation referred to as multiple lymphomatous polyposis. Leukemic involvement occurs in ~20–30% of patients overall, and a subset of patients may present with leukemic disease in the absence of significant adenopathy.

In the classic form of the disease, the neoplastic cells are small to intermediate in size with irregular, angulated nuclear contours, scant cytoplasm, and mature chromatin with indistinct nucleoli (Figure 6).[58–60] Three main growth patterns are identified: diffuse, nodular, and mantle zone. In the diffuse pattern, which is the most common, the nodal architecture is effaced by a diffuse infiltrate of small neoplastic cells, often admixed with epithelioid-appearing histiocytes. The differential diagnosis in such cases includes CLL/SLL, but proliferation centers are not identified in MCL. In the nodular growth pattern, the neoplastic cells form large nodules that may become confluent, and may create a differential diagnosis with FL. Lastly, the mantle zone pattern, which is the least common, shows hyperplastic GCs surrounded by a widened mantle zone that contains the neoplastic cells. The mantle zone pattern creates a differential diagnosis with reactive follicular hyperplasia, and the findings may occasionally be missed in the absence of phenotypic studies if one does not note the presence of widened mantle zones.

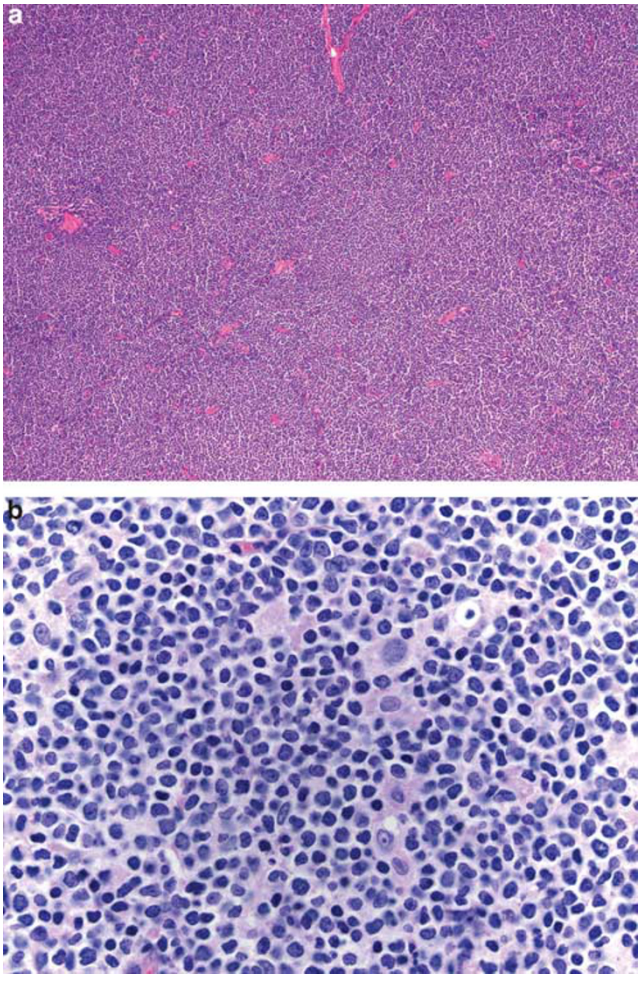

Figure 6 Morphology of MCL. (**a**) This case displays a predominantly diffuse lymphoid infiltrate. (**b**) At high magnification, the infiltrate is composed of small lymphocytes with angulated nuclear contours and scattered histiocytes.

Two aggressive variants of MCL are defined by their cytological features.[59,61–63] In the blastoid type, the cells are small to intermediate in size with finely dispersed chromatin, resembling lymphoblasts. This variant frequently displays prominent mitotic figures. In the pleomorphic type, the cells are intermediate to large with more irregular contours and vesicular chromatin, frequently resembling centroblasts. Such cases are easily misdiagnosed as diffuse large B-cell lymphoma, if Cyclin D1 immunohistochemical staining or *CCND1* FISH or molecular studies are not performed. Cases displaying either of these variant cytological patterns have been associated with a more aggressive clinical course. In addition, some cases may show cytological features intermediate between classic and blastoid or pleomorphic variants.[63,64]

MCL is typically positive for the B-cell markers CD19 and CD20 with surface immunoglobulin light chain restriction, positive for CD5, FMC7, and Cyclin D1, and negative for CD23. Absence of CD5 expression has been reported in a minority of cases, perhaps 5–10% of MCL overall.[65] A newer marker useful in the differential diagnosis of MCL is SOX11, which is positive in >90 of cases and may be particularly helpful if Cyclin D1 staining is suboptimal or otherwise difficult to interpret.[47,66] SOX11 expression has also been reported in cases recently identified as Cyclin D1-negative MCL (see Variant—Cyclin D1 Negative MCL section). SOX11 expression however is not unique to MCL and may also be seen in lymphoblastic lymphoma, Burkitt lymphoma, and T-cell prolymphocytic leukemia.[47]

The cytogenetic hallmark of MCL is the t(11;14)(q13;q32) *IGH*/*CCND1* translocation, which is identified in >95% of cases.[67–69] Variant translocations involving *CCND1* may also occur in a minority of cases, such as those involving *IGK* or *IGL* loci.[70] *CCND1* translocation results in overexpression of the Cyclin D1 protein, promoting cell cycle progression and proliferation. *CCND1* translocations can be identified by metaphase cytogenetics, PCR, or FISH.[18] At initial diagnosis, FISH studies generally yield the highest detection rate. FISH studies utilizing a *CCND1* break-apart

strategy are particularly valuable as these may also detect the other rare *CCND1* translocations other than the *IGH*/*CCND1*.

Variant—Cyclin D1 Negative MCL

Until recently, essentially all cases of MCL were assumed to carry a translocation involving *CCND1*. More recently, however, cases of Cyclin D1-negative MCL have been identified. The existence of Cyclin D1-negative MCL has been demonstrated on the basis of gene expression profiling studies that showed a gene signature identical to that in typical MCL, but lacking *CCND1* dysregulation.[71,72] Follow-up studies have confirmed the existence of cases of MCL that show morphological and phenotypic findings identical to that in MCL, except for the absence of Cyclin D1 staining.[45,47,73,74] Many of these cases appear to show dysregulation of *CCND2* or *CCND3*, sometimes due to translocations of these genes.[71,74,75] Recent studies have indicated that these cases, like typical MCL, are positive for SOX11.[47,66] Although formal criteria for the diagnosis of Cyclin D1-negative MCL have not yet been established, this diagnosis should currently be reserved for cases showing typical histological features of MCL, expression of CD5 and SOX11, and lack of Cyclin D1 staining and *CCND1* translocations by FISH (Figure 7).

Variant—Indolent MCL

Although MCL typically displays an aggressive natural history, a minority of cases have recently been noted to display a remarkable indolent clinical course.[76,77] These patients present with leukemic involvement, splenomegaly, and minimal if any adenopathy. Metaphase cytogenetic analysis typically shows t(11;14) as a simple karyotype, in contrast to overt MCL, which usually shows complex karyotypic abnormalities. Some reports have also indicated that these cases lack SOX11 expression. These patients may survive many years without therapy, and may be candidates for 'watch and wait' management approaches.

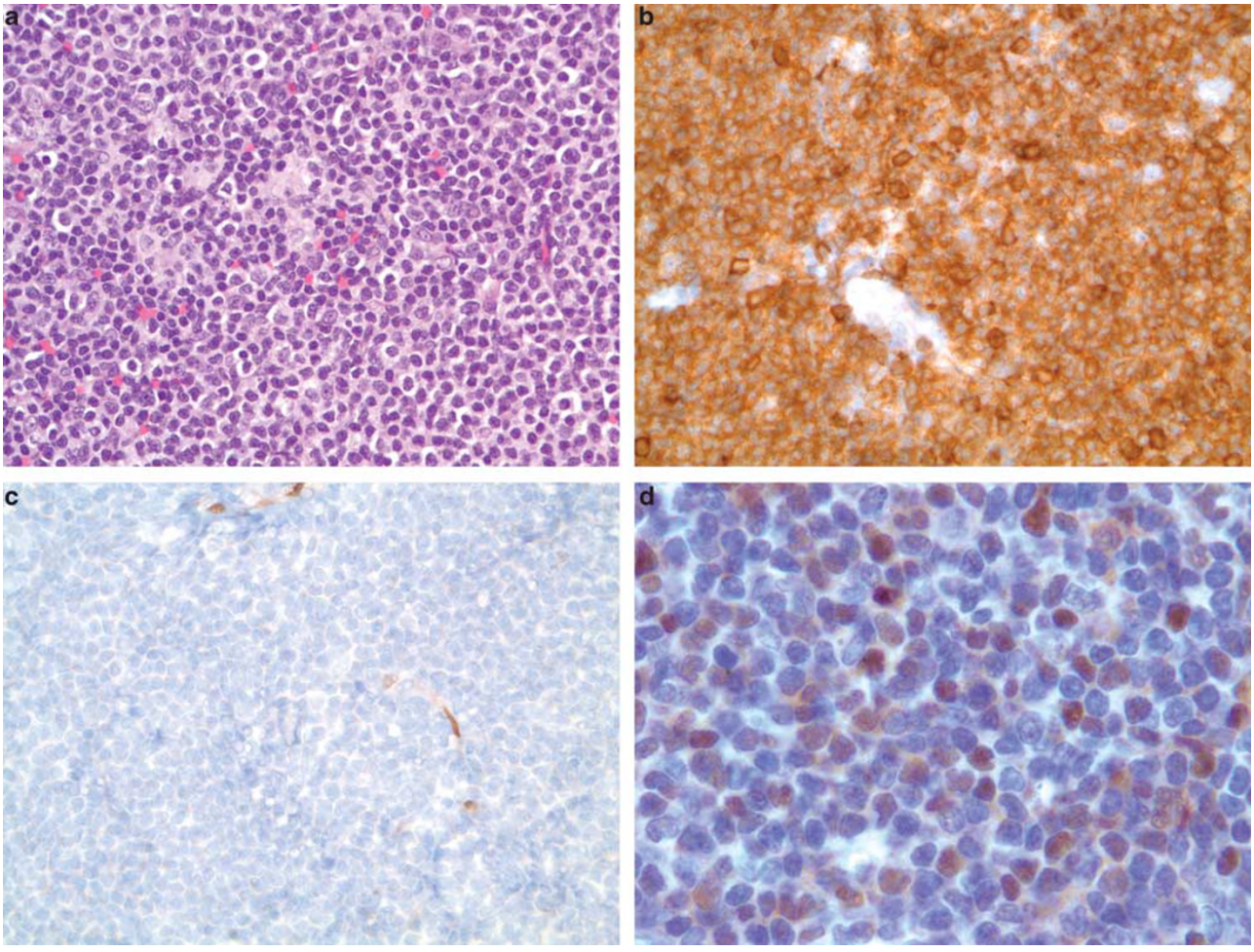

Figure 7 Cyclin D1 negative MCL. (**a**) On H&E, this case displays morphological features typical of MCL. (**b**) The B-cells coexpress CD5. (**c**) The B-cells are negative for Cyclin D1 (note positive staining in endothelial cells). (**d**) The B-cells show nuclear positivity for SOX11.

Precursor Lesion—MCL *In Situ*

As with the *IGH*/*BCL2* translocation, the presence of very low levels of *IGH*/*CCND1* fusion transcripts can also be detected by sensitive PCR techniques in a small subset of apparently healthy controls.[78] The tissue equivalent of this phenomenon is seen in occasional lymph node biopsies with completely preserved lymph node architecture, but focal GCs that are surrounded by mantle zones containing CD5-positive, Cyclin D1-positive B-cells (Figure 8).[2,79] In contrast to cases of MCL with a mantle zone growth pattern, cases of MCL *in situ* usually do not have widened mantle zones. If the mantle zones are widened, the Cyclin D1-positive cells are only a subset of the cells present within the mantles. Because of the minimal morphological changes in such cases, this phenomenon is essentially always detected only incidentally after Cyclin D1 immunohistochemistry. Cases of MCL *in situ* have been reported to express SOX11 less often than overt MCL.[2,66,79]

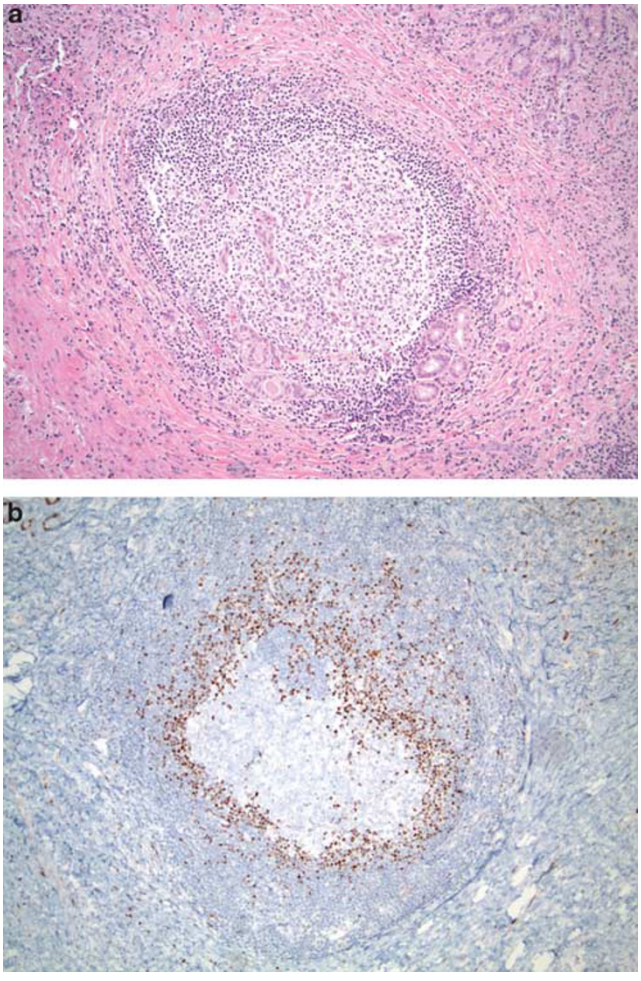

Figure 8 *In situ* MCL (**a**) H&E sections of a salivary gland lesion with fibrosis and scattered hyperplastic GCs, consistent with chronic inflammation. (**b**) A Cyclin D1 stain demonstrates positive B-cells lining the inner mantle zone of the GC.

Nodal marginal zone lymphoma

Primary NMZL is a nodal small B-cell neoplasm that resembles lymph nodes secondarily involved by marginal zone lymphoma (MZL) of extranodal or splenic types, but without extranodal or splenic involvement. NMZL is uncommon, representing 1–2% of NHL. The median age of presentation is in the eighth decade, and there is a female predominance ($\sim$1:5).[80,81] By definition, extranodal sites and spleen are not involved.

The malignant cells of NMZL consist of varying proportions of small mature lymphocytes, marginal zone-like cells, plasma cells, and cells resembling monocytoid B-cells (Figure 9).[81–83] Three growth patterns have been described: nodular, perifollicular, and diffuse. The nodular growth pattern, which is the most common, results from malignant cells surrounding and colonizing reactive GCs. In some cases, the nodularity may not be initially apparent in routine sections, but is readily identified by immunohistochemical staining for GC antigens and FDCs. In the perifollicular pattern, the tumor cells surround reactive GCs in a marginal zone distribution, but colonization of follicles is minimal. Lastly, the diffuse cases show sheets of tumor cells, often monocytoid in appearance, in the absence of reactive GCs.

A particularly difficult challenge in MZL is an assessment of the number of large cells present and their significance.[84] Unlike FL, there is no accepted scheme for grading of MZL. It may often be difficult to determine whether large cells scattered throughout represent large neoplastic cells or residual centroblasts from colonized GCs. In most cases, large cells represent $<$20% of the total cellularity. Some studies have suggested that even cases with 20–50% large cells do not behave in a

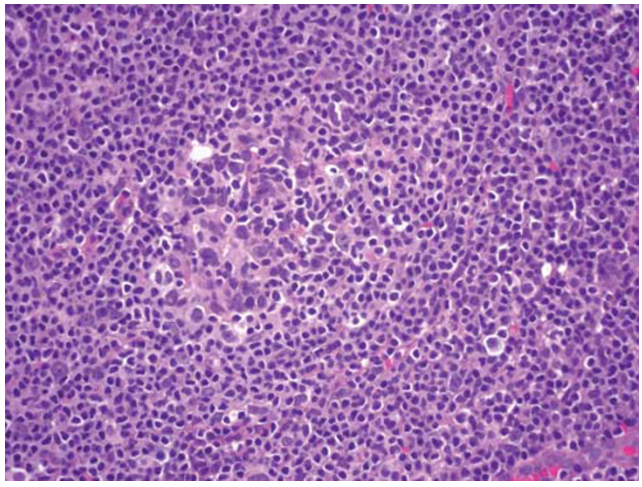

Figure 9 Morphology of NMZL. On H&E, this NMZL shows small lymphocytes with irregular nuclear contours and scant to moderate amounts of cytoplasm. The neoplastic cells invade and colonize a residual GC. Monocytoid cells in this case are uncommon.

more aggressive fashion.[85] For this reason, transformation to diffuse large B-cell lymphoma should only be diagnosed in the presence of sheets of large cells.

Phenotypically, most cases are positive for B-cell antigens and BCL2, and aberrant CD43 expression is observed in approximately half of cases.[81] CD5 expression, although not typical, has been reported in a minority of cases.[84] Distinction between CD5-positive MZL and SLL may be particularly challenging, and often rests on the presence or absence of proliferation centers and/or colonized follicles. MZL is negative for CD10, BCL6 and Cyclin D1. Plasmacytic differentiation is sometimes prominent, creating a challenging differential diagnosis with LPL.

The most common recurrent abnormalities include trisomy of chromosomes 3, 12, and 18.[85] Unfortunately, none of these abnormalities are specific for NMZL. Translocations involving the *MALT1* gene, as seen in a subset of extranodal MALT lymphoma, are not present.

Variant—Pediatric NMZL

Cases of NMZL arising in children or young adults show distinctive clinical features, including a marked male predominance of ~20:1.[86] These cases have a differential diagnosis with atypical marginal zone hyperplasia, which also occurs in this age group, resembles marginal zone lymphoma, and shows lambda light-chain restriction by flow cytometry but is non-clonal by molecular studies.[87] For this reason, PCR studies may be particularly valuable to distinguish between these two entities. Even when clonal, however, cases of pediatric NMZL appear to show an excellent clinical course with conservative therapy.

Lymphoplasmacytic lymphoma

LPL is a neoplasm of small B cells, plasmacytoid lymphocytes, and plasma cells that does not meet criteria for any other entity. LPL therefore remains in

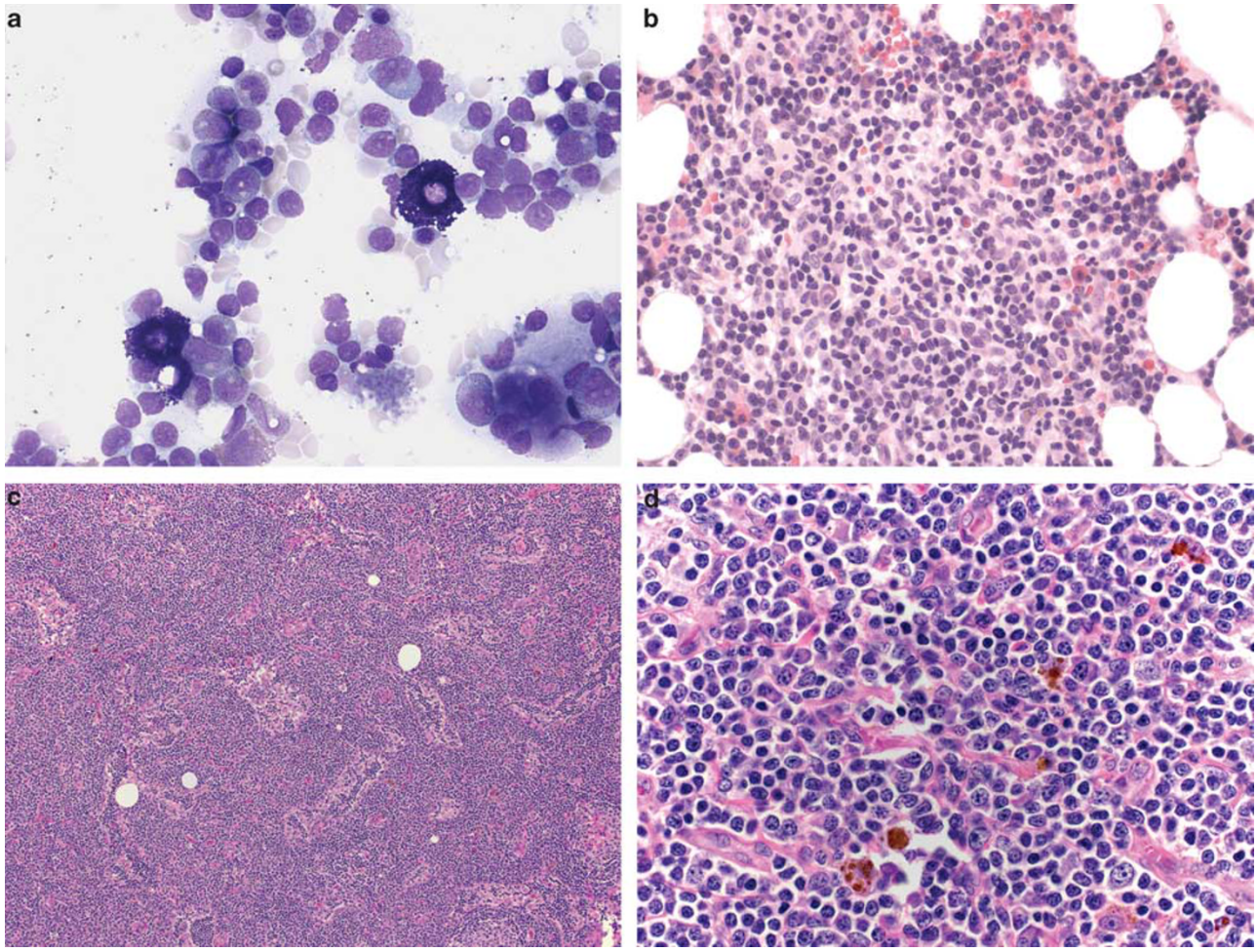

Figure 10 Morphology of LPL. (**a**) A bone marrow aspirate displays small lymphocytes, plasmacytoid lymphocytes, plasma cells and mast cells. (**b**) A bone marrow core biopsy shows an interstitial aggregate of small lymphocytes and plasma cells. (**c**) This lymph node shows partial architectural preservation with patent sinuses and a diffuse lymphoid infiltrate. (**d**) On high magnification, the infiltrate is composed of small lymphocytes and plasma cells with hemosiderin deposition.

part a diagnosis of exclusion. In particular, distinguishing LPL from NMZL with plasmacytic differentiation can be very challenging. Nevertheless, a confident diagnosis of LPL can be rendered in cases that show the classic features described below.

LPL typically presents in the seventh decade, and there is a slight male predominance.[88–90] Presenting symptoms include cytopenias related to bone marrow involvement and adenopathy. Most cases are associated with an IgM monoclonal protein, but this is not required for this diagnosis and LPLs expressing IgG or IgA heavy chains also occur. In patients with a high-level of IgM protein, there may be serum hyperviscosity, coagulopathy, and neuropathy.

Most cases of LPL are diagnosed on bone marrow biopsy, where one finds aggregates of small lymphocytes, plasmacytoid lymphocytes and plasma cells (Figure 10a and b).[88–90] Increased mast cells are frequently found within aggregates, but these are neither sensitive nor specific for this entity. In lymph nodes, several patterns of involvement have been described.[88,90,91] The most classic pattern consists of lymph nodes containing a diffuse infiltrate of small lymphocytes and plasma cells with largely preserved architecture and patent sinuses (Figure 10c and d). Cases displaying this pattern are highly associated with IgM paraproteins and bone marrow involvement. Other cases have been described as showing a 'vaguely nodular, polymorphous' pattern with effacement of the nodal architecture by a vaguely nodular proliferation of small lymphocytes, plasmacytoid cells, plasma cells, and variable numbers of large transformed cells and histiocytes. As with NMZL, there is no established method of 'grading' LPL, and a diagnosis of transformation to DLBCL should be reserved for cases showing sheets of large transformed cells.

LPL is usually reported to be negative for CD5, CD10, and CD23. However, aberrant expression of any of these antigens may be seen in a minority of cases.[92] The finding of aberrant CD5 expression is particularly challenging, as this raises the possibility of CLL/SLL with plasmacytic differentiation. Unfortunately, currently there are no specific phenotypic markers for LPL.

Translocations involving *IGH* are very rare, if seen at all, in LPL.[93] The most common recurring cytogenetic abnormality is del(6q), a nonspecific finding that may be seen in many other entities including NMZL.[90,91] Cytogenetic analysis usually does not assist in the distinction of LPL from NMZL or other small B-cell lymphomas with plasmacytic differentiation. Recently, a recurrent mutation in *MYD88* (*MYD88* L265P) has been described in a high proportion of LPL and in only a small minority of cases diagnosed as NMZL.[94,95] Additional studies will be required to determine the utility of this finding in routine diagnosis and classification of LPL.

Conclusions

The nodal and leukemic small B-cell lymphomas continue to present a frequent diagnostic challenge for the surgical pathologist. New immunohistochemical markers have emerged, which can assist in diagnosis and classification of challenging cases, but there continues to be an ongoing need for additional specific phenotypic or genotypic markers. Diagnostic criteria will also continue to evolve over time. In particular, the increasing recognition of the early lesions discussed above can be expected to be reflected in future classification schemes, which should assist practicing pathologists in guiding clinicians to the most appropriate therapies for their patients.

Disclosure/conflict of interest

The authors declare no conflict of interest.

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