The Pathology of Reactive Lymphadenopathies
A Discussion of Common Reactive Patterns and Their Malignant Mimics

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- Context.—Distinguishing between a reactive and a neoplastic lymphoid proliferation is a clinically significant task frequently performed by the surgical pathologist in routine practice.

Objectives.—To highlight common situations in lymph node pathology where reactive changes and lymphoma may be misdiagnosed.

Data Sources.—Data sources are peer-reviewed journal articles, textbooks, and clinical experience.

Conclusions.—This review aims to refresh and enhance the surgical pathologist’s awareness of the shared and distinguishing features of select reactive and neoplastic lymphoproliferations, which in turn will allow the surgical pathologist to make more accurate diagnoses and avoid the pitfalls of misdiagnosis. This will be done by describing a selection of commonly encountered reactive histologic changes observed in lymph nodes, present the lymphomas with which they share overlapping features, outline the features that distinguish them, and describe an approach to making an accurate diagnosis and avoiding a misdiagnosis in each scenario.


Lymph nodes are frequently encountered specimens in surgical pathology practice, and distinguishing the reactive lymph node from a neoplastic lymphoproliferative process is one of the many important roles the pathologist plays in patient care. Familiarity with the histologic changes that occur in reactive lymph nodes is important in preventing misdiagnosis of lymphoma, just as awareness of the histologic changes that lymphoid neoplasms share with reactive changes is key to not missing a diagnosis of lymphoma. A detailed description of all of the reactive lymphadenopathies and the lymphomas that can resemble them is beyond the scope of this work, and the reader is referred elsewhere for more detailed information.1–4 The purpose of this brief work is to refresh and enhance the practicing surgical pathologist’s awareness of the shared and distinguishing features of reactive and neoplastic lymphoproliferations, which in turn will lead to more accurate diagnoses and avoid the pitfalls of misdiagnosis. Herein, this is achieved by describing select common histologic changes encountered in lymph nodes, illustrating their overlapping features with malignant lymphoproliferations, highlighting the distinguishing features that permit accurate diagnosis, and describing a pathologic approach to avoid the pitfall of misdiagnosis.

LYMPH NODE STRUCTURE AND FUNCTION

To understand the features that distinguish reactive changes from neoplastic lymphoproliferations, one must be familiar with normal lymph node structure and function. The lymph node is a small oval or bean-shaped nodular structure made up of lymphoid tissue that filters circulating lymph and participates in immune reactions as part of the immune system. It is a highly organized structure composed of 4 main anatomic compartments: the cortex, paracortex, medulla, and sinuses (Figure 1, A).

The cortex lies within the periphery of the lymph node beneath the lymph node capsule. It is densely populated by B cells and organized into nodular structures called follicles (Figure 1, B). Depending on their state of antigen stimulation, follicles may be designated either primary or secondary. Primary follicles are composed of antigen-naïve, small mature B cells. Secondary follicles form when primary follicles react to antigen stimulation and are characterized by a peripheral mantle zone of small mature B cells surrounding a central germinal center made up of antigen-selected centroblasts and centrocytes that segregate into polarized dark and light zones, respectively, with admixed tingible body macrophages and follicular dendritic cells (Figure 1, C).

The paracortex is the T-cell–rich area that lies between B-cell follicles and extends deep into the cortex (Figure 1, D). The paracortex predominantly consists of small mature T cells as well as variable numbers of large transformed immunoblasts (T cells or B cells), interdigitating dendritic

Accepted for publication April 20, 2016.
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The authors have no relevant financial interest in the products or companies described in this article.
Portions of this work were presented at the Canadian Anatomic and Molecular Pathology Conference; January 29–30, 2016; Whistler, British Columbia, Canada.
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Arch Pathol Lab Med—Vol 140, September 2016
cells, plasmacytoid dendritic cells, and high endothelial venules (Figure 1, E).

The medulla is the most central region of the lymph node, lying adjacent to the lymph node hilum. It is arranged into cords that surround the medullary sinuses and contains a mixture of small B and T lymphocytes, plasmacytoid lymphocytes, plasmablasts, and mature plasma cells (Figure 1, F).

Figure 1. Lymph node structure and cellular constituents. A, (a) cortex, (b) paracortex, (c) medulla, and (d) sinuses. B, CD20 immunohistochemical stain highlighting B cells mainly in primary and secondary follicles and the medulla. C, Secondary follicle with a reactive germinal center showing polarization into (a) dark and (b) light zones. D, CD3 immunohistochemical stain highlighting T cells mainly in the paracortex and medulla. E, Paracortex composed of numerous small mature T lymphocytes, scattered interdigitating dendritic cells, occasional immunoblasts (short arrow), and high endothelial venules (long arrow). F, Medulla (long arrow) with numerous small lymphocytes and admixed plasma cells surrounded by a sinus (short arrow) containing histiocytes and scattered small lymphocytes and occasional granulocytes (hematoxylin-eosin, original magnifications ×20 [A] and ×200 [C, E, and F]; original magnification ×20 [B and D]).
Finally, the sinuses are endothelium-lined vessels that traverse the lymph node and carry lymph through the node parenchyma. Lymph carried in the afferent lymphatic vessel enters the node through the subcapsular sinus and traverses the node through the intermediary and medullary sinuses before finally emptying into the efferent lymphatic vessel and traveling away from the lymph node. Cells commonly seen in lymphatic sinuses include histiocytes, lymphocytes, plasma cells, and granulocytes (Figure 1, F).

Reactive changes in lymph nodes are typically classified into histologic patterns based on which of the aforementioned anatomic compartments is most prominently affected: follicular/nodular, which affects the cortex; interfollicular/paracortical, which affects the paracortex; sinusoidal, which affects the sinuses throughout the lymph node; and diffuse, which affects 2 or more of the anatomic compartments. This article will focus on 2 of the most commonly encountered changes, both of which have a follicular/nodular pattern: follicular hyperplasia and progressive transformation of germinal centers (PTGC), and the lymphomas that resemble them.

**FOLLICULAR HYPERPLASIA**

Follicular hyperplasia is the most common reactive change encountered in the lymph node. Often it is a nonspecific finding of unknown etiology; however, it can be seen in the setting of specific etiologies that have unique associated histopathologic findings, including infection (eg, human immunodeficiency virus, Epstein-Barr virus, toxoplasmosis, syphilis), autoimmune disease (rheumatoid arthritis, systemic lupus erythematosus), Castleman disease, or immunoglobulin G4 (IgG4)–related disease. It is beyond the scope of this work to outline the histopathologic features of each specific etiology, but the reader is referred elsewhere for more detail and encouraged to familiarize himself or herself with these specific disease entities. Follicular hyperplasia is characterized by an expansion of the cortex due to an increase in both the number and size of secondary follicles, with occasional extension into the paracortex and medulla (Figure 2, A). Importantly, follicular hyperplasia does not efface normal lymph node architecture, and the other lymph node compartments, although relatively diminished in size, are still recognizable. Reactive follicles may show variability in size and shape but typically exhibit polarized germinal centers that are made up of centroblasts and centrocytes with admixed tingible body macrophages and small mature lymphocytes, which are cuffed by well-formed and defined mantle zone (Figure 2, B and C). Immunohistochemical stains show that by far most lymphocytes in reactive lymph nodes, which are cuffed by well-formed and defined mantle zone cells, are CD20+ B cells. Germinall center B cells are positive for CD10 and BCL6 and negative for the antipapoptosis protein BCL2, whereas mantle zone B cells are positive for IgD and BCL2 and lack expression of CD10 and BCL6 (Figure 2, D through F). Reactive germinal centers also contain scattered small CD3+ follicular helper T cells that coexpress CD4, CD57, PD1, and BCL2. These T cells are more prominent in the germinal center light zone. CD21 highlights well-formed meshworks of follicular dendritic cells throughout follicles.

Two lymphomas that share histologic features with follicular hyperplasia and may be misdiagnosed as such are follicular lymphoma and mantle cell lymphoma.

**Follicular Lymphoma**

Follicular lymphoma is the most common indolent B-cell lymphoma in the Western world. 5 It primarily affects lymph nodes and characteristically shows expansion of the cortex and effacement of normal architecture by a proliferation of neoplastic B cells in a follicular pattern, sometimes with extension into perinodal fat (Figure 3, A). Neoplastic follicles are closely packed with attenuation or loss of their mantle zones. Their back-to-back growth leads to compression of the interfollicular space and loss of other lymph node compartments. At high power, follicular lymphoma is composed of a mixture of centrocytes and centroblasts: grades 1 to 2 disease contains 15 or fewer centroblasts per high-power field, whereas grade 3 disease contains more than 15 centroblasts per high-power field. Grade 3A disease retains centrocytes, whereas 3B consists of centroblasts only. 5 Malignant follicles show a loss of polarity with a haphazard distribution of centrocytes and centroblasts as well as reduced numbers of tingible body macrophages (Figure 3, B). Immunohistochemical stains show the neoplastic lymphocytes, both within and outside of follicles, are CD20+ B cells that express the germinal center B-cell proteins CD10 and BCL6 (Figure 3, C and D). Importantly, because of an underlying t(14;18)(q32;q21) IGH-BCL2 present in approximately 85% of follicular lymphomas, the malignant B cells typically overexpress BCL2 (Figure 3, E). 6,7 The proliferation index, by Ki–67 staining, varies with grade: grades 1 to 2 disease is typically less than 30%, whereas grade 3 disease is usually greater than 30%. There is a loss of polarity, with a more even and peripheralized staining pattern noted. Finally, CD21 highlights expanded but intact follicular dendritic cell meshwork within neoplastic follicles.

Distinguishing follicular lymphoma from follicular hyperplasia is straightforward, provided the pathologist pays close attention to the low- and high-power features and performs adequate immunohistochemical stains. Loss of normal architecture, close packing of uniform follicles, extranodal extension of follicles, cellular monomorphism, and BCL2 expression by B cells in germinal centers all favor a diagnosis of follicular lymphoma. However, in some situations not all of these features are present, and follicular lymphoma may be misdiagnosed as follicular hyperplasia.

Detection of BCL2 expression in germinal centers by immunohistochemistry is perhaps the most relied upon method for diagnosing follicular lymphoma in routine surgical pathology practice. BCL2 is expressed in approximately 85% of all follicular lymphomas because of the presence of an underlying t(14;18)(q32;q21), which places the BCL2 gene on chromosome 18 under control of the constitutively active promoter of the IGH gene on chromosome 14. However, 15% of follicular lymphomas do not express BCL2, and absence of BCL2 expression in germinal centers is not diagnostic of follicular hyperplasia, nor does it exclude a diagnosis of follicular lymphoma. Of particular note, grade 3A follicular lymphoma, which contains a mixture of centrocytes and centroblasts, and grade 3B follicular lymphoma, which contains centroblasts only, can resemble reactive germinal centers and are negative for BCL2 in upward of 50% of cases, which can easily lead to a misdiagnosis of follicular hyperplasia if only a cursory evaluation of the lymph node is performed. 6,8,9 The surgical pathologist needs to interpret negative BCL2 staining in conjunction with the low- and high-power morphologic features. If a germinal center exhibits atypical features,
including cellular monomorphism, loss of polarity, or decreased/absent tingible body macrophages or mitotic figures, the index of suspicion for a diagnosis of lymphoma should remain high and further testing should be performed, including immunohistochemical staining for immunoglobulin light chains and/or molecular genetic testing to look for evidence of a monoclonal B-cell population. Correlation with the results of flow cytometry is also useful in this situation; however, the reader must remain cautious because monoclonal B-cell populations can rarely be
Figure 3. Follicular lymphoma. A, Neoplastic follicles extending into perinodal fat. B, A neoplastic follicle showing loss of normal polarity and cellular monomorphism due to a homogeneous proliferation of malignant centrocytes (grade 1). C, CD20 immunohistochemical stain shows B cells within and between malignant follicles. D, CD10 immunohistochemical stain shows expression by B cells within and between malignant follicles. E, BCL2 (Epitomics E17 antibody [Abcam]) immunohistochemical stain is positive and aberrantly expressed by CD10+ B cells within and between follicles. F, BCL2 (Dako 124 antibody) immunohistochemical stain is negative in BCL2+ follicular lymphoma. G, Lymph node involved by in situ follicular neoplasia showing normal architecture with normally distributed follicles. H, BCL2 immunohistochemical stain showing aberrant strong expression in follicles involved by in situ follicular neoplasia (hematoxylin-eosin, original magnifications ×20 [A and G] and ×200 [B]; original magnification ×20 [C through F, and H]).
Figure 4. Mantle cell lymphoma. A, Lymph node involved by mantle cell lymphoma in a mantle zone pattern showing expanded mantle zones surrounding residual germinal centers. B, CD20 immunohistochemical stain shows marked expansion of mantle zones by B cells. C, CD5 immunohistochemical stain shows aberrant weak expression by abnormal B cells in mantle zones. Background T cells show normal strong expression of CD5. D, Cyclin D1 immunohistochemical stain shows expression by abnormal B cells in expanded mantle zones. E, CD10 immunohistochemical stain is positive in residual germinal centers. F, BCL2 immunohistochemical stain is negative in residual germinal centers. G, Lymph node involved by
detected both by flow cytometry and molecular genetic studies in histologically reactive lymphoid proliferations. Special mention should also be made of pediatric-type follicular lymphoma. This variant of follicular lymphoma typically occurs in, but is not restricted to, pediatric-age males, and it presents with localized disease usually involving a neck lymph node but occasionally Waldeyer ring or, rarely, the testis. It is characterized by large expansile follicles that efface lymph node architecture, and are composed of intermediate-sized blastoid centroblasts that express CD10 and BCL6 with a high proliferation index. It is a clonal lymphoid proliferation but does not harbor a t(14;18), and most cases lack expression of BCL2. As such, it may be misdiagnosed as grade 3 follicular lymphoma, but the diagnosis should not be missed, because unlike grade 3 follicular lymphoma, it has a good prognosis and behaves indolently, even without chemotherapeutic intervention.

BCL2 negativity in follicular lymphoma may also arise when the BCL2 protein does not express the epitope recognized by the BCL2 antibody—so-called pseudonegative BCL2 expression. Using a combination of BCL2 antibodies can increase the rate of detecting BCL2 protein expression by immunohistochemistry, and for this reason lymph nodes with BCL2-negative germinal centers that exhibit features suspicious for follicular lymphoma should be restained using another antibody that targets a different BCL2 epitope. Two useful BCL2 antibodies for immunohistochemistry are the 124 antibody made by Dako (Carpinteria, California) and the E17 antibody made by Epitomics (Abcam, Cambridge, Massachusetts).

BCL2 immunohistochemistry is also helpful in detecting in situ follicular neoplasia that may otherwise go undetected with morphologic evaluation alone. Unlike partial lymph node involvement by follicular lymphoma, which shows architectural effacement and abnormal follicles, in situ follicular neoplasia preserves the normal lymph node architecture and exhibits normally sized follicles with an intact, well-demarcated mantle zone. Importantly, in situ follicular neoplasia exhibits a monomorphic proliferation of centrocytes confined to germinal centers (Figure 3, G) that exhibit overexpression CD10 and BCL6. The definitive way to identify in situ follicular neoplasia is with a BCL2 immunohistochemical stain, which shows strong overexpression in centrocytes in one or more follicles (Figure 3, H). Prior to making a diagnosis of in situ follicular neoplasia, the surgical pathologist must be sure to compare the BCL2 stain to the CD3 stain because resident follicle center T cells normally express BCL2. When BCL2-positive cells exceed CD3+ cells and the pathologist is certain B cells are expressing BCL2, in situ follicular neoplasia should be suspected. Additionally, in situ follicular neoplasia cells usually exhibit stronger BCL2 expression than surrounding T cells, which is another helpful discriminatory feature. The identification of in situ follicular neoplasia is significant because up to one-half of patients are reported to harbor prior or concurrent lymphoma, and approximately 5% of patients will go on to develop it. The pathologist needs to be aware of this and alert the ordering physician to this possibility so the patient can be appropriately managed.

Mantle Cell Lymphoma

Mantle cell lymphoma is an uncommon B-cell non-Hodgkin lymphoma that usually involves lymph nodes. It grows in several architectural patterns, including mantle zone, nodular, and diffuse patterns (Figure 4, A). Classically, the malignant lymphocytes in mantle cell lymphoma are small to medium in size and monomorphic, but they differ from benign mantle zone cells in their increased nuclear contour irregularity, dispersed chromatin, and inconspicuous nucleoli. Immunohistochemical stains show the neoplastic lymphocytes in mantle cell lymphomas are CD20+ B cells that are usually positive for CD5 and negative for CD23. Importantly, because of an underlying t(11;14)(q13;q32) CCND1-IGH, the malignant B cells always overexpress cyclin D1 (Figure 4, B through D). The median survival of mantle cell lymphoma is approximately 3 to 6 years with current therapies, but few patients are cured of disease; therefore, distinguishing mantle cell lymphoma from follicular hyperplasia is of great clinical importance.

Mantle cell lymphoma growing in mantle zone pattern may be easily mistaken for follicular hyperplasia because the malignant lymphocytes grow at the periphery of follicles in an expanded mantle zone but leave unaltered the central germinal center, which shows the usual reactive features described above (Figure 4, E and F). Close inspection of the size and cellular composition of mantle zones around reactive follicles is required to prevent a missed diagnosis. Detection of cyclin D1 expression by immunohistochemistry is the best method for detecting and diagnosing mantle cell lymphoma in such cases. However, when interpreting a cyclin D1 stain the surgical pathologist needs to be aware that histiocytes and endothelial cells scattered throughout the lymph node, as well as some lymphocytes within reactive germinal centers, will show weak cyclin D1 expression and should not be overinterpreted as immunohistochemical evidence of mantle cell lymphoma. Mantle cell lymphoma typically shows strong uniform expression by the malignant lymphocytes.

Cyclin D1 negativity in mantle cell lymphoma will arise in rare cases that do not harbor the characteristic t(11;14). In such cases, studies have shown that mantle cell lymphoma will express the SOX11 protein. In cases with morphologic features suspicious for mantle cell lymphoma but negative for cyclin D1, additional immunohistochemical staining for SOX11 is required.

Cyclin D1 immunohistochemistry is also helpful in detecting in situ mantle cell neoplasia that would otherwise go undetected with morphologic evaluation alone. In situ mantle cell neoplasia preserves normal lymph node architecture and exhibits normal unexpanded mantle zones (Figure 4, G). The definitive way to identify in situ mantle cell neoplasia is with a cyclin D1 immunohistochemical stain, which typically shows strong expression among B cells within the inner half of the mantle zone (Figure 4, H). Most of the time, identification of in situ mantle cell neoplasia is an incidental finding with very indolent behavior; however,
Figure 5. Progressive transformation of germinal centers (PTGC). A, Two follicles showing early (top right) and more progressed (middle) stages of PTGC in a background of follicular hyperplasia (left). B, A progressively transformed germinal center showing infiltration by several small mantle zone B cells displacing background centroblasts and centrocytes; large atypical lymphocytes are not present. C, Immunoglobulin D immunohistochemical stain showing mantle zone expansion and inward migration of mantle zone B cells into progressively transformed germinal centers of 2 follicles. D, BCL6 immunohistochemical stain showing germinal center B cells displaced by inwardly migrating mantle zone B cells in 2 progressively transformed germinal centers. E, PD1 stain showing even distribution of follicular helper T cells in progressively transformed germinal centers compared with the polarized distribution seen in normal germinal centers; T-cell rosettes are absent (top left). F, CD21 immunohistochemical stain showing expanded follicular dendritic cell meshworks in progressively transformed germinal centers (hematoxylin-eosin, original magnifications ×20 [A] and ×200 [B]; original magnification ×20 [C through F]).
a subset of these patients either have or will go on to develop overt systemic mantle cell lymphoma. Much like in situ follicular neoplasia, the pathologist needs to be aware of this and alert the ordering physician to this possibility so the patient can be further evaluated.

In summary, when confronted with a possible diagnosis of follicular hyperplasia, the surgical pathologist must be sure to exclude the diagnoses of both follicular lymphoma and mantle cell lymphoma. Close evaluation of the low- and high-power architectural and cytomorphologic fea-

Figure 6. Nodular lymphocyte–predominant Hodgkin lymphoma. A, Lymph node showing vaguely macronodular architecture. B, Four large LP cells in a background of small mature lymphocytes; centrocytes and centroblasts are absent. C, CD20 immunohistochemical stain highlighting scattered LP cells and abundant small mantle zone B cells within the background. D, PAX5 immunohistochemical stain showing strong staining in LP cells as well as highlighting numerous small mantle zone B cells in the background. E, PD1 immunohistochemical stain highlighting T-cell rosettes around scattered LP cells. F, CD21 immunohistochemical stain showing expanded follicular dendritic cell meshworks in macronodules (hematoxylin-eosin, original magnifications ×20 [A] and ×200 [B]; original magnifications ×200 [C through E] and ×20 [F]).
Figure 7. Lymphocyte-rich classical Hodgkin lymphoma. A, Lymph node showing effacement of architecture by a nodular infiltrate. B, Scattered Hodgkin and Reed-Sternberg (HRS) cells that closely resemble centroblasts and LP cells in a background of small mature lymphocytes. C, CD30 immunohistochemical stain showing uniform membranous and Golgi expression by HRS cells. D, PAX5 immunohistochemical stain showing weak expression by HRS cells and strong expression by background mantle zone B cells. E, CD15 immunohistochemical stain is focally positive in HRS cells. F, CD20 immunohistochemical stain is negative in HRS cells. G, PD1 immunohistochemical stain highlighting scattered follicular helper T cells forming partial rosettes around HRS cells. H, CD21 immunohistochemical stain highlighting expanded follicular dendritic cell meshworks within nodules (hematoxylin-eosin, original magnifications ×20 [A] and ×200 [B]; original magnifications ×200 [C through G] and ×20 [H]).
natures with judicious but contextually appropriate use of ancillary studies, such as BCL2 and cyclin D1 immunohistochemistry, are required. The pathologist must also be aware of the clinical significance of detecting in situ lymphoid neoplasias and include this information in his or her reports.

**PROGRESSIVE TRANSFORMATION OF GERMINAL CENTERS**

Compared with follicular hyperplasia, PTGC is a less frequent but still commonly encountered reactive change seen by surgical pathologists in lymph node specimens. Progressive transformation of germinal centers usually presents with localized lymphadenopathy, although rarely it can be part of a systemic process with multiple lymph node groups involved. It affects men more often than women and young adults more frequently than children or the elderly. Histologically it is usually seen as a localized change in a background of follicular hyperplasia but can occasionally be seen as a generalized or florid process. Progressive transformation of germinal centers is characterized by expansion of the cortex by very large macronodules of enlarged secondary follicles with expanded mantle zones that show progressive and multifocal inward migration of mantle zone cells into the germinal center, which leads to germinal center disruption and eventual obliteration (Figure 5, A). In the late stages of progression the transformed germinal centers consist almost entirely of small mantle zone cells with only scattered centroblasts and centrocytes visible (Figure 5, B). Immunohistochemical stains show the small mantle zone cells are CD20+ B cells that are positive for IgD and BCL2, and negative for CD10 and BCL6 (Figure 5, C). Residual germinal centers B cells are positive for CD10 and BCL6, and negative for BCL2 (Figure 5, D). CD57+, PD1+ follicular helper T cells are also present and are evenly distributed throughout the germinal center, which is in contrast to the polarized distribution seen in the germinal centers of hyperplastic follicles (Figure 5, E). T-cell rosettes are not typically seen in PTGC. CD21 highlights expanded follicular dendritic cell meshworks that show disruption in the later stages of progression (Figure 5, F).

Progressive transformation of germinal centers has an unknown etiology; it is a benign entity but has a known association with nodular lymphocyte–predominant Hodgkin lymphoma (NLPHL) in a minority of cases, either as concomitant disease or as disease occurring before or after the discovery of PTGC. The surgical pathologist should keep this association in mind when evaluating a lymph node with PTGC and be sure to exclude additional involvement by lymphoma. Thus, when PTGC is identified in a lymph node it is important to go back to the gross pathology laboratory and submit the entire lymph node for comprehensive histologic evaluation to exclude focal involvement by lymphoma. The surgical pathologist should also bring the known association of lymphoma with PTGC to the attention of the referring physician and recommend biopsy of any other enlarged lymph nodes and close clinical follow-up if there is a clinical suspicion of malignancy. Additionally, lymphocyte-rich classical Hodgkin lymphoma shares overlapping features with PTGC and NLPHL and risks being underdiagnosed and inadequately treated without adequate evaluation.

**Nodular Lymphocyte–Predominant Hodgkin Lymphoma**

Nodular lymphocyte–predominant Hodgkin lymphoma accounts for approximately 5% of all Hodgkin lymphomas and affects young to middle-age men with greatest frequency. Nodular lymphocyte–predominant Hodgkin lymphoma nearly always involves lymph nodes, and patients usually present with localized low-stage disease. Histologically, NLPHL is characterized by effacement of the normal lymph node architecture by an atypical cellular proliferation in a nodular and variably diffuse pattern. Nodules are large (macronodules) and closely packed, with poorly defined borders (Figure 6, A). They are composed mostly of small mature lymphocytes. Importantly, scattered among the small lymphocytes are large malignant cells of NLPHL called LP cells. These cells have folded or multilobulated nuclei that harbor multiple basophilic nucleoli (Figure 6, B). Sometimes LP cells can resemble the malignant Hodgkin and Reed-Sternberg (HRS) cells of classical Hodgkin lymphoma. Follicular dendritic cells are present in nodular areas, and scattered epitheloid histiocytes are often seen, sometimes forming rings around macronodules. Granulocytes and plasma cells are characteristically absent. Immunohistochemical stains show LP cells are CD20+ B cells that are positive for CD45 and other pan-B–cell markers, including CD79a, PAX5, OCT-2, and BOB1 (Figure 6, C and D). LP cells may be positive for EMA, are rarely positive for CD30, and are always negative for CD15. The background small lymphocytes are a mixture of CD20+, IgD+ mantle zone B cells and CD3+ T cells. CD57+, PD1+ follicular helper T cells almost always form circumferential rosettes around LP cells (Figure 6, E). CD21 highlights expanded follicular dendritic cell meshworks within macronodules (Figure 6, F).

Several features help distinguish NLPHL from PTGC. In NLPHL, neoplastic macronodules replace the entire lymph node, thus effacing normal architecture; background follicular hyperplasia is usually absent. In addition, the macronodules of NLPHL frequently exhibit poorly delimited edges, whereas the transformed follicles of PTGC are well defined. Most importantly, LP cells are present in NLPHL and absent in PTGC, although scattered large centroblasts in PTGC may be mistaken for LP cells. EMA immunohistochemistry is helpful in identifying LP cells in cases where it is expressed. Residual large germinal center centroblasts present in late-stage PTGC may be mistaken for LP cells morphologically but are always negative for EMA. Also helpful are stains for CD57 and PD1, which nearly always highlight T-cell rosettes around the malignant LP cells but not around benign germinal center centroblasts.

**Lymphocyte-Rich Classical Hodgkin Lymphoma**

Lymphocyte-rich classical Hodgkin lymphoma shares many overlapping clinical features with NLPHL. It occurs with similar frequency, most often affects young to middle-age men, and presents with low-stage disease involving peripheral lymph nodes. Histologically, two patterns are identified: nodular and diffuse. The nodular pattern is far more common and is characterized by partially preserved or effaced lymph node architecture by an atypical lymphoid proliferation in a nodular pattern (Figure 7, A). Nodules are composed mostly of expanded mantle zones made up of small mantle zone cells and occasional to rare large HRS cells, which can resemble LP cells (Figure 7, B). Small and eccentrically located germinal centers are variably present in
malignant nodules but importantly do not harbor HRS cells. Other inflammatory cells, including granulocytes and plasma cells, are absent. Immunohistochemistry shows HRS cells are positive for CD30 (Figure 7, C) and weakly positive for PAX5 (Figure 7, D). They are usually positive for CD15 (Figure 7, E), usually negative for CD20 (Figure 7, F), and always negative for CD45. They also almost always lack expression of one or both of the B-cell transcription factors OCT-2 and BOB.1, unlike malignant LP cells, which consistently express both proteins.28 Background small lymphocytes are mostly CD20+, IgD+ mantle zone B cells. Scattered PD1+ T cells are also present and can form rosettes around HRS cells but do so less frequently than in NLPHL and are absent in nearly a quarter of cases (Figure 7, G).22 CD21 highlights intact follicular dendritic cell meshworks within neoplastic nodules (Figure 7, H).

Distinguishing lymphocyte-rich classical Hodgkin lymphoma from NLPHL and PTGC has important prognostic and therapeutic consequences. It requires careful evaluation of the lymph node and depends on the identification and demonstration of malignant HRS cells. In cases where HRS cells are rare or resemble centroblasts, other histologic features may lead to a misdiagnosis of PTGC, wherein cases where HRS cells resemble LP cells a misdiagnosis of NLPHL may be made. It is therefore of utmost importance to perform sufficient immunohistochemical staining that permits identification of malignant lymphocytes and discrimination between HRS cells and LP cells. A recommended approach is to perform a diligent low- and high-power morphologic evaluation of the lymph node to search for malignant lymphocytes, with judicious use of immunohistochemical stains for CD45, CD5, CD20, PAX5, OCT-2, BOB.1, CD30, CD15, EMA, IgD, CD57, PD1, and CD21.

CONCLUSION

Evaluation of reactive lymph node is not without folly, and the surgical pathologist needs to be aware of the potential pitfalls to avoid a missed diagnosis of lymphoma. Being aware of the differential diagnoses and potential mimics of reactive changes and having a sound morphologic and immunohistochemical approach to discriminating the benign from the malignant will ensure more accurate diagnoses and further support quality patient care.

References