Diffuse Large B-Cell Lymphoma—More Than a Diffuse Collection of Large B Cells
An Entity in Search of a Meaningful Classification

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• Context.—Diffuse large B-cell lymphoma is a heterogeneous group of lymphomas. In this review, we present a brief description of the large number of entities recognized in the recently published (2008) World Health Organization classification of tumors of hematopoietic and lymphoid tissues.

Objective.—We highlight the unique clinicopathologic and molecular genetic features of these new and previously recognized entities, to illustrate the rational for the development of this classification. To help simplify the understanding of this now large and complex group of diseases, we have attempted to create broader subgroups of related entities. We discuss large B-cell lymphoma that are not otherwise specified, those that are based on anatomic site, those that have unique histology or phenotype or genetic features associated with these subtypes of lymphoma.

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M ost reviews on diffuse large B-cell lymphoma (DLBCL) begin with a statement reiterating this type of lymphoma to be the most common lymphoid malignancy in adults. The statement belies the heterogeneity of the entities lumped in this catchall category that was traditionally defined based on morphology alone. Even though the “Revised European-American Classification of Lymphoid Neoplasms,” published in 1994, incorporated genetics and immunophenotype into the classification of lymphomas, the diagnosis of DLBCL continued to be defined by morphology. With a few exceptions, this remained largely unchanged in the 2001 World Health Organization (WHO) classification, which was essentially an update of the “Revised European-American Classification of Lymphoid Neoplasms” with no paradigm shift as far as DLBCL was concerned. The significant differences between the “Revised European-American Classification of Lymphoid Neoplasms” classification and the WHO classification were the recognition of intravascular large B-cell lymphoma (LBCL) and primary effusion lymphoma (PEL) as entities distinct from the rest of the DLBCL. Multianalytic (thymic) LBCL was recognized as a unique entity in the “Revised European-American Classification of Lymphoid Neoplasms” and retained its identity in the 2001 WHO classification. However, this still left DLBCL as a fairly heterogeneous group of lymphomas, where the only common feature was “diffuse proliferation of large neoplastic B lymphoid cells with nuclear size equal to or exceeding normal macrophage nuclei or more than twice the size of a normal lymphocyte.” The most recent WHO classification of tumors of hematopoietic and lymphoid tissues, published in 2008, has attempted to tease out specific entities from the DLBCL group (Table). However, most of these lymphomas continue to be defined by their nuclear size and fall into the somewhat “orphan” category of DLBCL, not otherwise specified (DLBCL, NOS). We present a brief description of the entities described as DLBCL in the current WHO classification, highlighting changes in the classification of DLBCL in the most recent WHO classification, along with the rationale for these changes. In contrast to the WHO classification, where the various entities are enumerated in no particular order, an attempt has been made to create subgroups: (1) those not otherwise specified; (2) those based on the anatomic location (site); (3) those based on histology, phenotype, or genotype; (4) those associated with Epstein-Barr virus (EBV) or Kaposi sarcoma–associated herpesvirus/human herpesvirus 8 (KSHV/HHV8); and (5) those that are considered unclassifiable (Table).

DIFFUSE LARGE B-CELL LYMPHOMA, NOT OTHERWISE SPECIFIED
As mentioned earlier, DLBCL, NOS, continues to be the most frequent type of DLBCL and accounts for 20% to 40% of the total incidence of lymphoma.
### Categories and Types of Large B-Cell Lymphoma

<table>
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<th>Category</th>
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<td><strong>Diffuse Large B-Cell Lymphoma (DLBCL), Not Otherwise Specified</strong></td>
<td>- Morphologic: centroblastic, immunoblastic, anaplastic, others&lt;br&gt; - Immunophenotype/gene expression: germinal center-derived, activated B cell, other&lt;br&gt; - Molecular/genetic: BCL6, BCL2, c-MYC, other</td>
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<td><strong>Large B-Cell Lymphoma Specified by Site</strong></td>
<td>- Primary mediastinal large B-cell lymphoma&lt;br&gt; - Intravascular large B-cell lymphoma&lt;br&gt; - Primary large B-cell lymphoma of bone&lt;br&gt; - DLBCL of the central nervous system&lt;br&gt; - Primary cutaneous large B-cell lymphoma, leg type</td>
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<td><strong>Large B-Cell Lymphoma Specified by Histology, Phenotype, or Genotype</strong></td>
<td>- T-cell/histiocyte-rich-B-cell lymphoma&lt;br&gt; - Anaplastic lymphoma kinase–positive large B-cell lymphoma&lt;br&gt; - De novo, CD3+ large B-cell lymphoma&lt;br&gt; - Large B-Cell Lymphoma (LBCL) Associated With Epstein-Barr Virus and/or Kaposi Sarcoma-Associated Herpesvirus/Human Herpesvirus 8&lt;br&gt; - EBV+ diffuse large B-cell lymphoma of the elderly&lt;br&gt; - DLBCL associated with chronic inflammation&lt;br&gt; - Pyothorax-associated lymphoma&lt;br&gt; - Plasmablastic lymphoma&lt;br&gt; - Primary effusion lymphoma&lt;br&gt; - LBCL arising in HHV8-malicentric Castleman disease and HHV8-plasmablastic lymphoma&lt;br&gt; - Lymphomatoid granulomatosis</td>
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<tr>
<td><strong>Unclassifiable Types</strong></td>
<td>- LBCL with features intermediate between DLBCL and Burkitt lymphoma&lt;br&gt; - LBCL with features intermediate between DLBCL and Hodgkin lymphoma</td>
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30% of all non-Hodgkin lymphoma (NHL) seen in adults. The median age at presentation is 70 years, but the lymphoma can occur in young adults and even in children. By definition, DLBCL, NOS, is a neoplasm of large B-cells with nuclear size equal to or exceeding macrophage nuclei reference range or twice the size of lymphocyte reference range, with a diffuse growth pattern. Before the diagnosis of DLBCL, NOS, is rendered, the possibility that the neoplasm represents one of the specific subtypes listed in the Table and discussed below should be excluded.

Extranodal presentation is common and almost one-third of the patients will have disease confined to extranodal sites at the time of diagnosis. The most common extranodal presentation is in the gastrointestinal tract, but involvement of other sites, including bone (see below), testis, spleen, Waldeyer ring, salivary gland, thyroid, liver, kidney, and adrenal gland, has been reported. Cutaneous lymphomas of large B-cell have seen several distinct biologic and clinical features and are not included in this category. For an overview of these lymphomas, the interested reader is referred to the synopsis of the WHO–European Organization for Research and Treatment of Cancer classification of cutaneous lymphomas.

Bone marrow involvement varies from 11% to 27% when routine microscopy alone is used for detection of disease. An additional 15% to 20% of patients have occult marrow involvement detectable by more sensitive techniques. Interestingly, almost half of the patients with bone marrow involvement have a discordant morphology, with the bone marrow showing involvement by a low-grade lymphoma, most commonly follicular lymphoma. Bone marrow involvement of greater than 10%, particularly when concurrent, is associated with a poor outcome. Histologically, the pattern of involvement in the lymph nodes and extranodal tissues is diffuse. Lymph nodes are usually entirely effaced, and the perinodal tissue is frequently infiltrated. Less frequently, lymph node involvement can be partial, with the involvement being interfollicular or sinusoidal. The morphology of the malignant cells is quite variable, and multiple, common, and not so common, variants are described. Conclusions about the biologic and prognostic significance of these morphologic variants are hampered by poor reproducibility and a lack of consensus amongst pathologists. In the 2001 WHO classification, the choice to incorporate the morphologic variant into the final diagnosis was left to the pathologist. Although the 2008 WHO classification discusses at length the more common morphologic variants of DLBCL, there is no discussion whatsoever of how this description should be dealt with in the final diagnosis. At our institution, it has been our policy to include all relevant information, including morphology and immunophenotype (as discussed below) in the synoptic diagnosis of DLBCL, NOS, if for no other reason than to facilitate subsequent data analyses. The common morphologic variants of DLBCL, NOS, are centroblastic, immunoblastic, and anaplastic. Less common or rare variants include the spindle cell variant, DLBCL with pseudorosettes, DLBCL with myxoid stroma, and DLBCL with fibrillar projections.

### Common Morphologic Variants

**Centroblastic Variant.**—The centroblastic variant of DLBCL, NOS, is the most common variant and comprises a predominant population of medium to large lymphoid cells with oval to round nuclei, vesicular chromatin, 2 to 4 nuclear membrane-bound nuclei, and scant to moderate amorphophilic cytoplasm (Figure 1, A). Variable numbers of immunoblasts may be present but are always less than 90% of the cells in the tumor. A variant of the centroblastic form is the centroblast with multilobated nuclei (Figure 1, B). Although seen most commonly in primary lymphoma of the bone (see below), this cytomorphology can also be seen in other extranodal sites.

**Immunoblastic Variant.**—The immunoblastic variant of DLBCL, NOS, must have greater than 90% immunoblast—large cells with large nuclei, vesicular chromatin, and single, large, centrally placed nucleoli (Figure 1, C). These cells usually have more abundant cytoplasm and can sometimes demonstrate plasmacytoid differentiation.

**Anaplastic Variant.**—The anaplastic variant of DLBCL, NOS, has large to very large cells, with pleomorphic nuclei that may, in part, resemble tumor cells of the anaplastic large cell lymphoma or even Reed-Sternberg cells (Figure 1, D). The pattern of lymph node involvement can be sinusoidal. However, the lymphoma is biologically distinct from the anaplastic lymphoma kinase–positive (ALK+) anaplastic large T-cell lymphomas or, for that matter, ALK+ B-cell lymphomas (discussed below). A plasmablastic form is another morphologic or cytologic variant of DLBCL, NOS (Figure 1, E), but it is more commonly considered to be in the EBV-related or ALK+ B-cell lymphoma categories, both of which are discussed below.
pressed with variable frequency; simultaneous expression followed by IgG and IgA. CD38 and CD138 can be expressed, immunoglobulin (Ig) M is expressed most frequently, face immunoglobulin may not be expressed. When present, immunoglobulin (lg) M is expressed most frequently, followed by IgG and IgA. CD38 and CD138 can be expressed with variable frequency; simultaneous expression of these 2 plasma cell antigens is not observed in CD20+ DLBCL. CD30 expression is seen in some cases and is particularly associated with an anaplastic morphology. CD5 expression can be seen in up to 10% of the patients with DLBCL. Although not considered a distinct entity in the 2008 WHO classification, we believe that these lymphomas have unique biology and clinical features and merit discussion as a distinct entity (see below). Variable numbers of small T cells can be present in the neoplasm. However, the diagnosis of T-cell–rich/histiocyte-rich DLBCL should be rendered only when the criteria for that entity are met (see below).

To better identify the various subtypes that might morphologically be lumped into the category of DLBCL, NOS, various groups have attempted to develop molecular signatures of these lymphomas (reviewed extensively in Shipp14). A cell-of-origin–based model can be proposed that can be predicted reproducibly and robustly by the expression pattern of as few as 27 genes. Based on this model, most DLBCL can be classified as germinal center derived or activated B cell derived. However, 2 problems remain: (1) the need to translate this gene expression into a meaningful, clinically applicable, laboratory-based test that can be used routinely; and (2) a small number of DLBCL cases cannot be accurately classified based on this model. Several groups have attempted to use commonly available antibodies to recapitulate this cell of origin based classification. The most extensively used and validated model is the “Hans classifier.” According to this model, cases with CD10 expression in greater than 10% of the cells are classified as germinal center derived. In addition, cases that are CD10+, but BCL6+ and interferon regulatory factor 4 (IRF4)/multiple myeloma oncogene-1 (MUM1) are also considered germinal center derived. All other cases are considered not germinal center derived. Although not necessarily overlapping with the gene expression profiles, the model was successful in prognostic classification of DLBCL, at least in the era before rituximab. At our institution, this panel is routinely used for all DLBCL cases and the subtype (germinal center vs not germinal center) included in the synoptic diagnosis.

**Genetics**

Several nonrandom chromosomal translocations have been reported in DLBCL. These involve BCL6 (35%–40% cases), BCL2 (13% translocations, 24% amplifications), c-MYC (15%), c-MYC (15%), c-MYC (15%), FAS (20%), and TP53 (16%) gene cases. In addition, about 45% of cases will demonstrate somatic hypermutations that target multiple germinal center genes, including BCL6, PIM1, c-MYC, PAX5, and RhoH/ITF.

Overall, the DLBCL, NOS, remains a heterogeneous category of aggressive lymphomas largely defined by the size of the malignant cells. However, as additional information continues to emerge on the biology of these lymphomas, there is an attempt to tailor the therapy of these lymphomas based on the biology. Even though the current therapy is largely determined by the stage of disease, we find it useful to include all relevant information, including relevant immunophenotype information, in the diagnosis. We strongly believe that this is crucial for meaningful data collection for subsequent analyses.

**LARGE B-CELL LYMPHOMA SPECIFIED BY SITE**

A major group of LBCLs is specified essentially by the primary site of involvement. Although there is some dis-
cussion as to whether these specific types are distinct from DLBCL, NOS, in general, and whether they constitute specific biologic entities, their unique presentation in most patients sets them apart and raises consideration of specific differential diagnoses that differ from the more typical nodal-based disease. Many of these site-specific types also have somewhat distinctive presentation, morphology, immunophenotype, and clinical course to further imply that they may indeed be distinct biologically.

**Primary Mediastinal Large B-Cell Lymphoma**

Primary mediastinal LBCL was first described in the 1980s. It is specific not only for its presentation in the mediastinum but also for its epidemiologic profile, its immunophenotype, and its molecular signature. Some believe that it has an improved prognosis compared with DLBCL, NOS, and that it has an unusual pattern of spread in patients with relapse.

Primary mediastinal LBCL occurs in a younger patient population than the more typical DLBCL because it is seen in younger adults between the age of 30 and 40 years and has a higher incidence in women (male to female ratio, 1:2). Because of the primary site, patients may present with superior vena cava syndrome, phrenic nerve palsy, dysphagia, hoarseness of voice, chest pain, or cough.

Biopsy interpretation can be challenging because the lymphoma is commonly associated with sclerosis, which can sometimes predominate over the malignant B-cell population, especially in small needle biopsies. The sclerosis is frequently present in large bands but also in finer strands that separate the malignant B cells into nests (Figure 2, A and B). The malignant B cells tend to be centroblastic and sometimes to have multilobation, which is considered by some to be a characteristic morphologic feature.

The B-cell nature of the large cells is easily determined by CD20 positivity, but proof of clonality by flow immunophenotyping is frequently not possible because expression of surface or cytoplasmic immunoglobulin is surprisingly absent. Another phenotypic distinction is the presence of CD30 on the large B cells. This, together with the sclerosis or fibrosis in the background, can mimic Hodgkin lymphoma, also a strong diagnostic consideration in a younger adult woman with a mediastinal mass. How-
biopsies are usually curettage specimens in which there is abundant crush artifact and insufficient material for ancillary studies, such as flow immunophenotyping and cytogenetic analysis. Although, as mentioned, a lymphoma primary in bone can be T anaplastic, lymphoblastic, or Burkitt lymphoma, the most common type and what is more likely a biologic entity, is primary large B-cell lymphoma of bone. These can have centroblastic or immunoblastic features, or more frequently, a centroblastic morphology with multilobated nuclei (Figure 2, D). This latter morphologic type, which in some series represents most cases, is quite striking, with large, sometimes excessively lobulated, nuclei. Phenotypically, the large B-cell lymphomas of bone are CD19+ and CD20+ and commonly have BCL6 and CD10 expression. Large series studied for cytogenetic abnormalities are lacking, but BCL2 is generally not rearranged.\textsuperscript{28}

Primary lymphoma of bone, particularly the large B-cell type, has a favorable prognosis. This may, in part, be due to the exclusion of higher-stage disease. Nevertheless, it seems that patients present with low-stage disease, with the tumor confined to the bone and to the adjacent soft tissue and that they do well, with an overall 5-year survival of 60% to 70%.\textsuperscript{29} Some reports note that there is worse survival in older patients and in those with immunoblastic morphology.
**Diffuse Large B-Cell Lymphoma of the CNS**

Nodal-based or extranodal DLBCL not infrequently disseminates to the CNS. Primary CNS large B-cell lymphoma must be distinguished from such cases with secondary spread. Central nervous system DLBCL is defined as a primary lymphoma of the intracerebral or intraocular areas, excluding those that are dural lymphomas, those that are immunodeficiency related, or as mentioned, those that are due to secondary spread. These lymphomas are rare and occur in all ages but peak in individuals in their sixth decade. Central nervous system DLBCLs usually involve the supratentorial areas (60% of the time) and produce cognitive dysfunction, psychomotor slowing, personality change, or disorientation.

Diagnosis can be complicated, and knowledge of steroid use is imperative. Steroids can cause lymphoma cells to disappear and a diagnosis after steroid treatment can sometimes be next to impossible. Stereotactic biopsy is the diagnostic procedure of choice, and the diagnosis rests on finding large B cells growing in cuffs around vessels in an angiocentric pattern (Figure 2, E and F). Apparently, the lymphoma cells have a predilection for perivascular growth.

In most cases, the large B cells have a centroblastic morphology and are CD19+, CD20+, and CD79a+. BCL6 is frequently positive, and CD10 is less so; IRF4/MUM1 is expressed in 80% to 90% of cases. If material is sufficient for flow analysis, the lymphoma cells will show monoclonal surface immunoglobulin. Epstein-Barr virus is consistently negative, in contrast to CNS lymphomas in immunocompromised individuals, particularly those with human immunodeficiency virus (HIV), in which EBV expression is quite common. Cytogenetic changes include translocations involving BCL6 (3q27) and common deletions of 6q and additions at 12q, 22q, and 18q21.30-32

Survival for patients with CNS DLBCL has been poor, but recent developments in advanced treatment strategies have improved survival so that patients may have a stable tumor response for several years.

**Primary Cutaneous Large B-Cell lymphoma, Leg Type**

It is well known that B-cell lymphomas can occur with a cutaneous presentation. Although most are relatively indolent, it became clear that a subset of cases were more aggressive. In an attempt to identify discriminating factors among what was a heterogeneous group of primary cutaneous B-cell lymphomas, investigators recognized that the location on the leg was a distinct major factor identifying the aggressive nature of a subset of cases. A WHO-European Organization for Research and Treatment of Cancer classification of primary cutaneous B-cell lymphomas now lists 3 major types of cutaneous B-cell lymphoma: primary cutaneous marginal-zone lymphoma, primary cutaneous follicular lymphoma, and primary cutaneous diffuse large-cell lymphoma, leg type, with the latter signifying the aggressive type.33

Primary cutaneous diffuse large-cell lymphoma, leg type, is now felt to be a distinct entity. It has an advanced age of onset, with a mean age of 76 years. It has a high predilection for the leg (72%) but can occur elsewhere. Lesions usually are cutaneous nodules or tumors and, less commonly, occur as plaques, subcutaneous masses, or ulcerations. Lesions are often multiple and can sometimes be present on both legs. Histologically, cases show centroblastic or, less commonly, immunoblastic features (Figure 2, G and H). Cases with increased centrocytes are excluded because they are more likely follicular lymphomas. Immunophenotypically, cases are classically BCL2− (unlike primary cutaneous follicular lymphoma, which is BCL2+), IRF4/MUM1+, and forkhead box P1 (FOXP1) positive.34

Clinically, primary cutaneous diffuse large cell lymphoma, leg type, is aggressive with a 5-year overall survival of 41%.35

**LARGE B-CELL LYMPHOMA SPECIFIED BY HISTOLOGY OR PHENOTYPE/GENOTYPE**

A smaller group of large B-cell lymphomas can be defined by their specific morphologic characteristics or by specific immunophenotypic/genotypic features. Although rare, those with unique molecular characteristics are quite likely distinct biologic entities.

**T-Cell, Histiocyte-Rich B-Cell Lymphoma**

The characteristic morphologic feature of T-cell, histiocytic-rich B-cell lymphoma is the abundant T-cell and histiocytic-host inflammatory reaction and the minor proportion (<10%) of malignant B cells in biopsy specimens. As such, the lymphoma must be distinguished from peripheral T-cell lymphoma and from Hodgkin lymphoma of either the classic or nodular lymphocyte predominant type.

T-cell, histiocytic-rich B-cell lymphoma is an uncommon variant of large B-cell lymphoma that occurs in somewhat younger patients, with a mean age of 46 years. It is predominant in men, has a higher incidence of B symptoms, and has a higher involvement of the spleen, liver, and bone marrow at presentation.36

The morphologic features include a diffuse effacement of the nodal architecture with a predominance of small T cells and histiocytes and scattered large cells with centroblastic, immunoblastic, or morphologic features resembling the “popcorn” cells of nodular lymphocyte-predominant Hodgkin lymphoma (Figure 2, I and J). Typically, the large cells are positive for CD45, CD20, and CD79a. The staining is critical for recognition of the B-cell nature of the minor large-cell component. The absence of staining for CD15 and CD30 helps distinguish the process from classic Hodgkin lymphoma and the absence of CD21+ follicular dendritic networks, as well as the vague nodules of B cells, helps distinguish it from nodular lymphocyte-predominant Hodgkin lymphoma. CD57+ rosettes, which frequently surround the lymphocytic and histiocytic cells of nodular lymphocyte-predominant Hodgkin lymphoma are also absent.37,38

Gene expression profiling has identified a “host response” profile, which is defined mostly by the expression of the reactive inflammatory cells, rather than by the malignant tumor cells. T-cell, histiocytic-rich B-cell lymphoma typically shows this “host response” pattern. However the pattern is also seen in approximately one-third of DLBCL, indicating that T-cell, histiocytic-rich B-cell lymphoma constitutes only a small subset with this expression type.

Although the prominent host reaction to the tumor cells would make one think that the process has a greater survival profile than cases without the T-cell or histiocytic reaction; in actuality, it is just as aggressive as DLBCL and should be treated similarly.
Anaplastic large cell lymphoma, with expression of anaplastic lymphoma kinase protein, is a specific type of NHL that typically has a T-cell or null-cell phenotype, associated commonly with a t(2;5)(p23;q35) or a variant translocation involving ALK, and characterized by anaplastic morphology. CD30 expression, and ALK overexpression in either a nuclear and cytoplasmic or dual distribution. In 1997, Delso described a small series of ALK+ large B-cell lymphomas; many of these were subsequently found to have a unique translocation involving ALK, the t(2;17)(p23;q23).

Anaplastic lymphoma kinase–positive large B-cell lymphoma usually has immunoblastic or plasmablastic morphology, rather than an anaplastic one (Figure 2, K and L). It typically lacks CD20 and CD79a staining and frequently only shows weak CD45 staining. The tumor cells express monotypic cytoplasmic immunoglobulin and are IgA or, less commonly, IgG. They are clonal by immunoglobulin gene-rearrangement analysis. The lymphoma involves commonly with a t(2;5)(p23;q35) or a variant NHL that typically has a T-cell or null-cell phenotype, as- sociated with a unique translocation involving ALK on band 17p23. Cryptic rearrangements of ALK or other kinases are frequently found to have a unique translocation also involving ALK, the t(2;17)(p23;q23).

\[ \text{ALK}^+ \text{ Large B-Cell Lymphoma} \]

CD5+ B-cell malignancies include SLL/CLL, the associated Richter transformation to large B-cell lymphoma, and mantle cell lymphoma with its blastoid variant. Large B-cell lymphoma, distinct from Richter transformation of SLL/CLL and mantle cell lymphoma, was described in 1995 by Matolcsy et al., and has since been referred to as de novo CD5+ large B-cell lymphoma.

Whether the process is truly distinct from other types of DLBCL is unclear, but the presence of intravascular or sinusoidal infiltration in a large percentage of cases indicates significant overlap at least with intravascular LBL. Remarkable morphologic heterogeneity has been recognized in this lymphoma, and 4 morphologic variants of this lymphoma have been described recently. These include a monomorphic type, a giant cell–rich type, a polymorphic type, and an immunoblastic type.

Immunophenotypically, CD5+ de novo LBCLs are usually BCL6+, CD10+, IRF4/MUM1+, and BCL2+ and thus are believed to be nongerminai-center–derived lymphomas. Genetic studies on a small number of cases conclude that, based on the higher incidence of deletion of D13S252, a frequent finding in SLL/CLL, de novo CD5+ LBCL may be derived from the same CD5+ progenitor as in SLL/CLL. Some survival studies have shown that de novo CD5+ LBCLs are more aggressive than CD5− cases and that CNS relapse is also high. We have observed that bone marrow involvement can be deceptive as the large neo-
Figure 3. Illustration of large B-cell lymphoma associated with Epstein-Barr virus (EBV) and/or Kaposi sarcoma–associated herpesvirus/human herpesvirus 8 (KSHV/HHV-8). A through D, EBV+ diffuse large B-cell lymphoma (DLBCL) of the elderly showing polymorphic proliferation of large, transformed lymphoid cells with occasional atypical, multinucleated, large cells, resembling Reed-Sternberg cells, and focal areas of necrosis (A) (hematoxylin-eosin, original magnification ×40). Large cells show expression of CD20 (B) (original magnification ×40), and positive hybridization signals with EBV-encoded RNA in situ hybridization (EBER/ISH; C) (original magnification ×40). Monomorphic subtype of DLBCL (D) (H&E, original magnification ×40). E through H, Plasmablastic lymphoma showing proliferation of immunoblasts displaying immunophenotypic features of plasma cells (E) (hematoxylin-eosin, original magnification ×40). Plasmablasts demonstrate CD138 expression (F) (original magnification ×40) hybridization signals with EBER/ISH (G) (original magnification ×40) but show no evidence of latent KSHV infection with immunostaining for open reading frame (ORF) 73 latent nuclear antigen (LNA-1 [LANA]; H) (original magnification ×40). I and J, Primary effusion lymphoma showing large, atypical cells with plasmablastic/anaplastic morphology displaying large nuclei, prominent nucleoli, and abundant basophilic cytoplasm. Some cells show perinuclear hof, consistent with plasmacytoid differentiation (I) (Wright-Giemsa, original magnification ×100). Large, atypical cells are strongly positive for latent KSHV infection with antibody to ORF 73 LNA-1 (LANA) performed on cells in a cell block (J) (original magnification ×50). K through M, HHV8+, multicentric Castleman disease (HHV8 MCD) and HHV8+, plasmablastic lymphoma (HHV8 PL). HHV8 MCD with scattered plasmablasts in the follicular mantle, demonstrating nuclear positivity for LANA and cytoplasmic expression of a light chain (inset and K) (ORF 73 LNA-1, original magnification ×20 [K] and ORF 73 LNA-1, brown, a light chain-red, double staining, original magnification ×40 [inset]). HHV8 PL showing sheets of atypical plasmablasts (L) (hematoxylin-eosin, original magnification ×40) that are strongly positive for latent KSHV infection with an antibody to ORF 73 LNA-1 (LANA; M) (original magnification ×40). N and Q, Lymphomatoid granulomatosis showing polymorphous infiltrate in the vascular wall (N) (hematoxylin-eosin, original magnification ×20) comprising scattered CD20+ large B cells (O) (original magnification ×20), and numerous CD3+, small T cells (P) (original magnification ×20). Large B cells show hybridization signals with EBER/ISH (Q) (original magnification ×20).
encoded RNAs (EBER; Figure 3, C). Epstein-Barr virus latent membrane protein 1 (LMP1) is detected in large neoplastic cells in 94% of cases and EBV nuclear antigen-2 in 28% of cases, thus indicating EBV latency type II and type III, respectively.45,46

Molecular techniques usually demonstrate clonal immunoglobulin gene rearrangement.45,46

The clinical course of EBV+ DLBCL of the elderly is aggressive, with median survival of about 2 years, irrespective of the subtype of lymphoma or the International Prognostic Index score. The presence of B symptoms and age older than 70 years appear to be the only reliable prognostic factors.46

DLBCL Associated With Chronic Inflammation

Diffuse large B-cell lymphoma associated with chronic inflammation is a DLBCL that arises in a setting of long-standing chronic inflammation and that shows strong association with EBV.45,51 In most patients, this lymphoma develops in body cavities or narrow spaces. A prototypic form of this lymphoma is pyothorax-associated lymphoma (PAL). This develops in the pleural cavity of patients with long-standing pyothorax, usually greater than 10 years, resulting from artificial pneumothorax for treatment of pulmonary or pleural tuberculosis or tuberculosis pleuritis.52,54 Diffuse large B-cell lymphoma associated with chronic inflammation can also arise in other settings of long-standing chronic suppuration/inflammation, such as chronic osteomyelitis or metallic implants in bone, joint, periarticular soft tissue, or chronic skin ulcer.55

Most cases of PAL occur in Japan, but some cases were reported in Western countries.56,57 Age at diagnosis ranges from fifth to eighth decade, with a mean age in the seventh decade of life. The male to female ratio is approximately 12.3:1.57

Pyothorax-associated lymphoma usually presents with a pleural mass larger than 10 cm in more than half of the patients and may invade into adjacent structures.58 However, at the time of diagnosis, the tumor tends to be confined to the thoracic cavity and presents in clinical stage I/II of disease in about 70% of patients.57 Clinical symptoms include chest or back pain, fever, tumor or swelling in the chest wall, or respiratory symptoms, such as productive cough, often with hemoptysis or dyspnea.57 Serum levels of C-reactive protein and lactate dehydrogenase are often highly elevated.57 Patients with lymphoma in the bone, joint, periarticular soft tissue, or skin usually present with pain or mass lesion.

Histologically, most cases of PAL display centroblastic/immunoblastic morphology and may demonstrate angiocentric growth and areas of necrosis. Neoplastic cells usually express CD20 and CD79a and variably CD30. A proportion of cases may display plasmacytic differentiation with expression of IRF4/MUM1 and CD138 and variable loss of CD20 and CD79a. Occasional cases may also express one or more of T-cell–associated antigens (CD2, CD3, CD4, and/or CD7), causing a problem with lineage assignment. Most cases are EBER+ by ISH and show EBV latency III (LMP1+ and EBV nuclear antigen 2+ by immunohistochemistry).53,54,58,59

Immunoglobulin genes in PAL are clonally rearranged and in some cases are hypermutated.60 Many cases show TP53 mutations.61 Cytogenetic studies reveal complex karyotypes with numeric and structural abnormalities. Gene expression profile of PAL is distinct from nodal DLBCL with differential expression of genes known to be involved in apoptosis, interferon response, and signal transduction.52 The postulated cell of origin in this lymphoma is an EBV-transformed, late-germinal center/postgerminal-center B cell.60

The clinical course of PAL is aggressive, with 5-year survival ranging from 20% to 35%. Pleurectomy or pneumonectomy, with or without resection of adjacent involved tissues, may offer good treatment results. Poor performance status and high serum levels of glutamic pyruvate transaminase and blood urea nitrogen were reported to be significantly associated with shortened survival.57,63

Plasmablastic Lymphoma

The current WHO classification recognizes plasmablastic lymphoma (PBL) as a distinct subtype of DLBCL. Plasmablastic lymphoma is defined as DLBCL in which neoplastic cells resemble B immunoblasts but show immunophenotypic features of plasma cells (Figure 3, E and F).4

Plasmablastic lymphoma occurs with highest incidence in HIV+ individuals but may arise in a setting of other immunodeficiency states such as posttransplant immunodeficiency, immunosuppressive therapy for autoimmune diseases, advanced age or primary immunodeficiency syndromes.64-68 Plasmablastic lymphoma mainly affects adults, with a median age of 50 years, but rare cases are reported in children with immunodeficiency. Plasmablastic lymphoma was first described in the oral cavity, where it occurs most frequently, but it may also occur in other extranodal sites, particularly mucosal areas, including sinonasal cavity, gastrointestinal tract, orbit, skin, bone, or soft tissue.64,66 Nodal involvement is uncommon, although PBL occurring in a setting of non-HIV immunodeficiency more commonly presents in lymph nodes.65 Most patients present with advanced, stage III or IV lymphoma with intermediate or high International Prognostic Index scores.64,66

Histologically, PBL demonstrates a morphologic spectrum ranging from those showing cells resembling immunoblasts to those with cells showing more distinct plasmacytic differentiation (Figure 3, E). The mitotic activity in PBL is usually high, and apoptotic cells and tingible body macrophages can be readily appreciated. Plasmaclastic lymphoma associated with HIV infection usually displays more monomorphous morphology and develops in mucosal sites (mucosal type), such as oral, nasal, or paranasal areas. Cases with plasmacytic differentiation tend to occur more commonly in other extranodal sites as well as lymph nodes.64,65 Plasmablastic lymphoma displays a plasma cell phenotype. It is positive for CD138, CD38, VS38c, and IRF4/MUM1 positivity. CD45 is usually negative or weakly positive. B-cell markers, such as CD20 or PAX5, are usually down-regulated, whereas CD79a may be positive. Monotypic cytoplasmic immunoglobulin (clg) of either κ light chain or λ light chain, and mostly IgG heavy-chain isotype, can be demonstrated in 50% to 70% of cases. Epithelial membrane antigen and CD30 are commonly expressed. CD56 may be positive in cases with plasmacytic differentiation, but oral PBL are usually CD56−. Ki-67 proliferation index is usually high (>90%). Epstein-Barr virus–encoded RNA can be demonstrated by ISH in 60% to 75% of cases and in almost 100% of the oral mucosal type of PBL. LMP1 is only rarely expressed, and there is consistently no evidence, to our knowledge, of KSHV/HHV8 (Figure 3, G and H).63,65,66,69

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Molecular techniques demonstrate clonal immunoglobulin gene rearrangement, which can show somatic hypermutation or be unmutated. Postulated cell of origin in PBL is a proliferating B cell that has switched its phenotype to that of plasma cell gene-expression profile.70

The clinical course of PBL is aggressive, with survival of less than 1 year.64–66 Recently, clinical outcome may have improved possibly because of better HIV management and more intensive therapy.71

Primary Effusion Lymphoma

Primary effusion lymphoma or body cavity lymphoma is an LBCL universally associated with KSHV/HHV8, usually presenting as a serous effusion without detectable tumor masses.4,72–74 Primary effusion lymphoma most often occurs in middle-aged, homosexual or heterosexual men with HIV infection, in a setting of severe immunodeficiency. Usually, in these cases, there is coinfection with EBV. Primary effusion lymphoma may also develop in recipients of solid organ transplant, in the absence of evident immunodeficiency, or in areas with high prevalence of KSHV infection, such as in the Mediterranean, in which case it may lack EBV coinfection.73–77

Primary effusion lymphoma most commonly involves pleural, pericardial, and peritoneal cavities and presents without detectable tumor masses or lymphadenopathy. Usually, only one body cavity is involved. Some patients with PEL may develop solid tumors in adjacent structures such as pleura. Rare cases of KSHV/HHV8–associated lymphoma, indistinguishable from PEL, may present as solid tumor masses in extranodal sites or lymph nodes without serous effusion and have been designated extracavitary PEL.4,78–79 Approximately 50% of the patients with PEL develop or have preexistent Kaposi sarcoma, and some patients have associated multicentric Castleman disease (MCD).80,81 Primary effusion lymphomas should be distinguished from rare cases of HHV8– effusion lymphoma showing similar morphologic features, which can occur in ascites of patients with liver diseases and in DLBCL associated with chronic inflammation (PAL).4,51–53

In cytospin preparations, PEL cells display variable morphology, ranging from large immunoblasts/plasmablasts to cells with more anaplastic morphology, and some cells may resemble Reed-Sternberg cells. Nuclei are large and rounded to more irregular, and nucleoli are prominent. Cytoplasm is abundant, and deeply basophilic, occasionally with vacuoles (Figure 3, I).73–78 In some cases, perinuclear hof may be observed, consistent with plasmacytoid differentiation.4,73,80 Primary effusion lymphoma cells appear more uniform in histologic sections than in cyt цentrifuge preparations.78,79 Primary effusion lymphoma cells usually express CD45 but lack expression of B-cell–associated antigens, such as CD19, CD20, PAx5 and CD79a. Surface immunoglobulins and clgs are usually absent or weakly expressed in a fraction of cells (usually of λ light chain isotype), and BCL6 is usually absent. Conversely, PEL cells express a variety of activation antigens, plasma cell–associated antigens, and nonlineage restricted antigens, such as HLA-DR, CD30, CD38, VS38c, CD138, IRF4/MUM1, and epithelial membrane antigen.73,80,83 Primary effusion lymphoma cells also express the B-lymphocyte–induced maturation protein (BLIMP1), a key regulator of terminal B-cell differentiation.83,84 Primary effusion lymphoma cells usually lack T/NK antigens, although some cases may show aberrant expression of T-cell markers.85,86

Primary effusion lymphoma cells express latent Kaposi sarcoma–associated antigen open reading frame (ORF) 73 latent nuclear antigen (LANA), which can be demonstrated by immunohistochemistry (Figure 3, J).85 Epstein-Barr virus can be demonstrated in cases coinfected with EBV using ISH for EBER, but LMP1 is usually not detected.4 Extracavitary PELs display similar phenotypic features to PELs, although they may show more frequent expression of B-cell–associated antigens and immunoglobulins.79

Molecular techniques demonstrate clonal immunoglobulin gene rearrangement in PEL, which is hypermutated. In some cases, T-cell receptor genes may also be rearranged.86,87 No recurrent chromosomal abnormalities have been identified. Gene expression profile of AIDS-related PEL revealed a distinct profile with features of both plasma cells and EBV-transformed lymphoblastoid cell lines, suggesting that PEL tumor cells correspond to a stage in B-cell development that is intermediate between that of immunoblasts and plasma cells.88 The mechanism by which KSHV/HHV8 promotes oncogenesis in PEL is an area of extensive investigation. Kaposi sarcoma–associated herpesvirus encodes a number of homologues to cellular genes that provide proliferative and antiapoptotic signals.4,89

The clinical course of PEL is aggressive, and prognosis is poor, with median survival shorter than 6 months.80,90 In retrospective studies, poor performance status and the absence of highly active antiretroviral therapy were identified as being independently associated with impaired clinical outcome in HIV-related PEL.92 Rare patients have responded to chemotherapy and/or immune modulation.53

LBCL Arising in HHV8-Associated Multicentric Castleman’s Disease

Human herpesvirus 8 causes a spectrum of lymphoproliferative lesions in patients with MCD, ranging from isolated HHV8 cells resembling plasmablasts to “microlymphoma” and frank plasmablastic lymphoma.94 Large B-cell lymphoma arising in HHV8-associated MCD is defined as a monoclonal proliferation of HHV8-infected lymphoid cells resembling plasmablasts, expressing IgM, and arising in the setting of MCD. It is also known as HHV8 plasmablastic lymphoma (HHV8 PL) or Kaposi sarcoma–associated herpesvirus–positive plasmablastic lymphoma.4 The neoplastic cells in HHV8 PL are consistently infected with HHV8/KSHV but show no evidence of coinfection with EBV. Human herpesvirus 8 infection can be demonstrated in neoplastic cells by immunohistochemistry with an antibody against HHV8-associated ORF 73 LANA, which shows characteristic stippled nuclear positivity.

Human herpesvirus 8 plasmablastic lymphoma occurs worldwide, more commonly in patients with HIV-associated HHV8 MCD and less commonly in HIV− patients with HHV8 MCD, usually in regions with high prevalence of HHV8 infection (Africa and the Mediterranean countries).95 Human herpesvirus 8 plasmablastic lymphoma typically involves lymph nodes and spleen but may disseminate to other organs via the bloodstream and rarely shows leukemic peripheral blood involvement. Patients with HHV8 PL typically present with profound immunodeficiency, enlarged lymph nodes, splenomegaly, and often, Kaposi sarcoma.94,96

Histologically, lymph nodes and spleen in HHV8 MCD
show a variable degree of lymphoid follicle involution and hyaline formation of germinal centers associated with expansion of the mantle zones, which may completely efface the germinal centers. Among the mantle zone cells, there is a variable number of LANA+ plasmablasts, which remarkably nearly always are positive for IgM light chain (Figure 3, K). HHV8 infected plasmablasts may also show variable expression of the viral interleukin 6 (v-IL6) and are CD20+, CD79a+, CD38+, CD27+, IRF4/MUM1+ and BLIMP1+, but lack expression of plasma cell associated marker CD138 and are consistently EBER+. The interfollicular areas contain numerous plasma cells, which are clgM−, clgA−, express polytypic light chains and are LANA−.8,9,94 With progression of disease, the plasmablasts expand and coalesce to form confluent clusters/aggregates of “microlymphoma” and in some cases may progress to frank HHV8 PL (Figure 3, L and M). Emergence of HHV8 PL manifests by prominent expansion of HHV8 infected plasmablasts, which completely efface the lymph node or splenic architecture.94

Although KSHV+ plasmablasts in MCD express monotypic IgM light chain, they are polyclonal by polymerase chain reaction-based analysis of immunoglobulin heavy-chain and λ light chain rearrangement.95 “Microlymphoma” may be polyclonal or monoclonal and the frank HHV8 PL is monoclonal. Both in HHV8 MCD and HHV8 PL the immunoglobulin genes are unmutated, thus indicating that they correspond to naive IgM producing plasma cells. Activation of the interleukin-6 receptor (IL-6R) signaling pathway has been implicated in pathogenesis of lymphoproliferative disorders arising in HHV8 associated MCD.99

Both HHV8 MCD and PL are highly aggressive disorders with a median survival of only a few months.94

Lymphomatoid Granulomatosis (LYG)

Lymphomatoid granulomatosis is included in this review because it is an EBV driven LPD that shares some morphologic and clinical features with EBV associated DLBCL and may progress to DLBCL.1

Lymphomatoid granulomatosis is an angiocentric and angiodestructive lymphoproliferative disease involving extranodal sites, comprised of EBV+ B cells admixed with numerous T cells and other inflammatory cells, which usually predominate (Figure 3, N through Q). Lymphomatoid granulomatosis shows a spectrum of histologic grade and clinical aggressiveness, which is related to the proportion of large EBV+ B cells to the relative lymphocyte background. Lymphomatoid granulomatosis (LYG) must be differentiated from natural killer T-cell lymphoma, nasal type. An underlying immunodeficiency, including primary or secondary immunodeficiency disorders, is a risk factor for developing LYG. Even immunocompetent patients usually demonstrate some degree of reduced immune function on careful clinical or laboratory evaluation. Lymphomatoid granulomatosis is uncommon and usually occurs in adults but may also be seen in children with immunodeficiency disorders.8,9,99 Lymphomatoid granulomatosis appears to occur more frequently in western countries than in Asia. It predominantly involves the lungs and, less frequently, the skin, kidney, liver, and CNS. Most commonly, it presents as pulmonary nodules, which frequently show necrosis and may cavitate.100,101 Nodular lesions are also seen in kidney and brain and are usually associated with necrosis. Skin lesions may present as nodular lesions in the subcutaneous tissue or dermal involvement with necrosis and ulceration. Less common are cutaneous plaques or maculopapular rashes.101–103 Clinical symptoms in LYG are variable and related to the site of organ involvement. Respiratory tract symptoms include cough, dyspnea, and chest pain. Constitutional symptoms include fever, malaise, weight loss, neurologic symptoms, arthralgias, and myalgias. Central nervous system involvement may be asymptomatic or may show varied presentation depending on the site of involvement or change in mental status.104 Asymptomatic disease is only rarely seen.103

Histologically, LYG shows variable morphology. There are usually a small number of EBV+ B cells in a prominent inflammatory background comprising numerous T lymphocytes, plasma cells, immunoblasts, and histiocytes. Neutrophils and eosinophils are usually inconspicuous. The EBV+ transformed B cells usually show some degree of atypia and may resemble immunoblasts; less commonly, they have a more pleomorphic appearance resembling Hodgkin cells or multinucleated forms. Classical Reed-Sternberg-like cells generally are not observed. Well-formed granulomas are usually absent in the lung and other extranodal sites.105 Skin lesions often exhibit granulomatous reaction in subcutaneous tissue.102 Vascular changes may be prominent with an infiltrate in the vascular wall, which may compromise vascular integrity and lead to infarct-like tissue necrosis. (Figure 3, N). Epstein-Barr virus can be demonstrated in B cells by EBER/ISH. Epstein-Barr virus–positive B cells usually are CD20+, CD30− (variable), and CD15−. LMP1 may be positive in larger atypical cells, and cIgM can be demonstrated in some cases, particularly when the B cell shows plasmacytoid differentiation. Background T cells are composed mostly of CD4+ T cells (Figure 3, O through Q).

Lymphomatoid granulomatosis is graded into grades 1 to 3 based on the proportion of large EBV+ B cells to the relative lymphocyte background.101,107 Grade 1 lesions are characterized by a polymorphous lymphoid infiltrate without cytologic atypia. Large, transformed cells are absent or rare, and necrosis is usually focal when present. Epstein-Barr virus–encoded RNA–positive cells account for less than 5 per high-power field. Grade 2 lesions show occasional large lymphoid cells/immunoblasts in a polymorphous background. Small clusters of CD20+ B cells may be seen, and necrosis is more frequently observed. Epstein-Barr virus–encoded RNA–positive cells are seen at a rate of 5 to 20 per high-power field and, occasionally, at up to 50 per high-power field.99 Grade 3 lesions are characterized by inflammatory background, but large atypical CD20+ B cells are readily appreciated and may form large aggregates. Markedly pleomorphic and Hodgkin-like cells are often present. Usually, there is extensive necrosis, EBER+ cells are numerous (>50/high-power field), and focialy they form small sheets.4

Molecular techniques demonstrate clonal immunoglobulin gene rearrangement in most grade 2 and grade 3 LYG lesions.101,106 Some cases may show different clonal populations in different anatomic sites.99 Epstein-Barr virus clonality can be demonstrated by Southern blot.108 Alterations of oncogenes have not been identified.

The clinical course of LYG is variable. In some patients, LYG has a waxing and waning course with rare spontaneous remission without therapy. In most patients, LYG is an aggressive disease, with a median survival of less than 5 years.104,105

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ly recognizes the B-cell origin of these lymphoid neoplasms and provides a guideline to the treating physician. By definition, the category includes B-lineage lymphomas that demonstrate overlapping clinical, morphologic, and immunophenotypic features between classic Hodgkin lymphoma and DLBCL. The most common site of involvement is the anterior mediastinum, but involvement of other sites has been reported.109

Morphologically, the lymphoma is typically composed of a confluent, sheeplike growth of pleomorphic tumor cells in a variably fibrotic stroma.110 A single tumor can have areas resembling classic Hodgkin lymphoma, a centroblastic variant of DLBCL or primary mediastinal B-cell lymphoma. The inflammatory infiltrate is usually sparse but can be variable and includes eosinophils, plasma cells, histiocytes, and T cells. Variable areas of necrosis can be seen frequently but are not associated with increased neutrophils.

The immunophenotype also shows an overlap between Hodgkin lymphoma and DLBCL. Thus, CD45 expression is present along with the expression of B-cell antigens, including CD20 and CD79a. Other B-cell antigens that are frequently expressed are Oct-2, BOB.1, and PAX5. CD10 is not expressed, and ALK expression is consistently absent. However, in contrast to other large B-cell neoplasms, these B-cell markers are expressed in conjunction with variable amounts of CD30 and CD15. In agreement with this overlapping phenotype between a classic Hodgkin lymphoma and a B-cell lymphoma, these lymphomas have a gene expression profile that is intermediate between DLBCL and Hodgkin lymphoma but closely resembles primary mediastinal B-cell lymphomas.111

Although there is no consensus on the optimal therapy protocols for these lymphomas with features intermediate between DLBCL and classic Hodgkin lymphomas, we believe the recognition of these lymphomas primarily as B-cell lymphomas will result in a more rational and uniform approach to treatment.

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CORRECTIONS

In the April 2009 issue of the Archives, some percents shown in 3 tables that appeared in an article from Lippi et al (Lippi G, Targher G, Montagnana M, Salvagno GL, Zoppini G, Guidi GC. Relation Between Red Blood Cell Distribution Width and Inflammatory Biomarkers in a Large Cohort of Unselected Outpatients. Arch Pathol Lab Med. 2009;133[4]:628–632) were incorrect. Specifically, in Table 2, the percent range for RDW quartile II should have been expressed as 13.0%–13.5%, the percent range for quartile III should have been 13.6%–14.6%, and the percent for quartile IV should have been ≥14.7%. In Table 3, the percent range for quartile II should have been 13.3%–13.8%, and the percent range for quartile III should have been 13.9%–14.9%. In Table 4, the percent range for quartile II should have been 13.0%–13.3%, and the percent range for quartile III should have been 13.4%–13.9%.

The last name of Sandeep Gurbuxani, MBBS, PhD, was incorrectly shown as Gurbaxani in the byline and affiliation footnote of an article that appeared in the July 2009 issue. The correct citation is Gurbuxani S, Anastasi J, Hyjek E. Diffuse Large B-Cell Lymphoma—More Than a Diffuse Collection of Large B Cells: An Entity in Search of a Meaningful Classification. Arch Pathol Lab Med. 2009;133(7):1121–1134.