Primary Cutaneous Diffuse Large B-Cell Lymphoma, Leg Type
Diagnostic Considerations

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Context.—Primary cutaneous diffuse large B-cell lymphoma, leg type, may show features that overlap with other lymphomas. However, timely recognition of this entity can have important clinical and therapeutic implications.

Objective.—To review the clinical, morphologic, and immunophenotypic characteristics of primary cutaneous diffuse large B-cell lymphoma, leg type, and juxtapose these features with other diagnostic considerations. In particular, other variants of primary cutaneous diffuse large B-cell lymphoma, as well as primary cutaneous follicle center lymphoma, will be reviewed. Additionally, systemic/extra-cutaneous lymphomas will be discussed, including diffuse large B-cell lymphoma, not otherwise specified, Epstein-Barr virus–positive diffuse large B-cell lymphoma of the elderly, and lymphomatoid granulomatosis.

Data Sources.—Relevant literature will be reviewed and key differentiating findings will be highlighted.

Conclusions.—Although primary cutaneous diffuse large B-cell lymphoma, leg type, may show aspects that overlap with other lymphomas, it can be distinguished from other entities in the differential diagnosis.

The first report of what is now known as primary cutaneous diffuse large B-cell lymphoma, leg type (PCDLBCL-LT), dates back to 1987.1 In a study of 19 patients with primary cutaneous large cell lymphomas, a group of elderly women with tumors on the lower legs were distinguished by a worse prognosis.1 Approximately 10 years later, so-called primary cutaneous large B-cell lymphoma of the leg was recognized as a unique diagnostic entity with exclusive involvement of the leg, an intermediate prognosis, and diffuse dermal infiltrate of large B-cells.2,3 These large B cells included large centrocytes, centroblasts, and B immunoblasts.2,3 Interestingly, it was noted that patients with a diffuse, monotonous infiltrate of centroblasts and/or immunoblasts had a worse prognosis.2 However, the current concept of PCDLBCL-LT did not emerge until a 2001 multicenter study4 examined prognostic factors in primary cutaneous large B-cell lymphomas. This study of 145 patients established that B-cell morphology had a significant impact on survival, regardless of site.4 In particular, patients with a predominance of large B cells with round nuclei (ie, centroblasts and immunoblasts) had a poorer prognosis, regardless of body location.5 This study provided the basis for the present diagnostic category of primary cutaneous diffuse large B-cell lymphoma, leg type.5

CLINICAL, MORPHOLOGIC, AND IMMUNOPHENOTYPIC FEATURES
PCDLBCL-LT most commonly involves the lower leg(s) of older women (male to female ratio of 1:2–4; median age in the 70s).6–10 However, other parts of the body are affected 10% to 20% of the time.7–10 Patients typically present with rapidly developing red to plum-colored nodules or tumors on one or both legs (Figure 1, A).7,8 Although, by definition, these lymphomas are limited to the skin at presentation, they often spread to extracutaneous sites, most commonly to the lymph nodes, the bone marrow, and the central nervous system.4,7,8 Approximately half of these patients will not survive 5 years, and those who present with multiple cutaneous tumors often do worse.4,7,8 Consensus guidelines recommend that these lymphomas be treated similarly to a systemic diffuse large B-cell lymphoma with an anthracycline-containing chemotherapeutic regimen, such as rituximab, cyclophosphamide, doxorubicin (adriamycin), oncovin (vincristine), and prednisone (R-CHOP), and possibly including involved field radiation therapy.11

Morphologically, PCDLBCL-LT is composed of diffuse, monotonous sheets of large B cells within the dermis that are separated from the epidermis by a grenz zone (Figure 1, B). These “large” B cells display nuclei that are more than twice the size of a normal lymphocyte or at least as large as a normal macrophage nucleus.8 In addition, they display what has been termed round cell morphology (Figure 1, C).4–6 This
round, nuclear morphology identifies the centroblasts and immunoblasts characteristic of this lymphoma and distinguishes these cells from the cleaved or irregular nuclear morphology of large centrocytes. Centroblasts typically display a round nucleus with open chromatin and 1 to 3 peripheral nucleoli. Immunoblasts also demonstrate a round nucleus, but have a single, central nucleolus and often show more abundant, basophilic cytoplasm. Mitotic figures are also often easily identified in PCDLBCL-LT. However, in contrast to primary cutaneous follicle center...
lymphoma (PCFCL, discussed below), T cells are relatively sparse.6,10

In addition to traditional B-cell markers (CD19, CD20, CD22, CD79a, PAX-5), PCDLBCL-LT classically expresses BCL2, IRF4/MUM-1, and FOXP1 (Figure 1, D through F). However, this immunophenotype is not specific to PCDLBCL-LT and may also be seen in other diffuse large B-cell lymphomas that secondarily involve the skin,6,12 or in uncommon cases of PCFCL.9,13 Moreover, its importance to establishing the diagnosis of PCDLBCL-LT is controversial. Some experts prefer not to categorize lymphomas that do not express BCL2 as PCDLBCL-LT, instead identifying these lymphomas as “primary cutaneous diffuse large B-cell lymphomas, other” (PCDLBCL-other).9,13 However, the World Health Organization (WHO) notes that approximately 10% of cases of PCDLBCL-LT do not express BCL2 or IRF/MUM1. Moreover, several studies have shown no correlation between prognosis and expression of BCL2, IRF4/MUM1, or FOXP1 in patients who meet morphologic and clinical criteria for PCDLBCL-LT.7,9,13 PCDLBCL-LT also commonly expresses BCL6, but typically lacks CD10.6,10 Additionally, a recent study14 identified immunoglobulin M (IgM) as another sensitive marker of PCDLBCL-LT.

DIFFERENTIAL DIAGNOSIS

Primary Cutaneous Diffuse Large B-Cell Lymphoma, Other

The 2005 WHO/EORTC (WHO/European Organization for Research and Treatment of Cancer) classification of cutaneous lymphomas defines the category of PCDLBCL-other as exceptional cases of large B-cell lymphoma that present in the skin, but do not meet diagnostic criteria for PCDLBCL-LT or PCFCL.5 Specifically, this classification system suggests that PCDLBCL-other should be used to describe rare cases of primary cutaneous T-cell and histiocytic-rich large B-cell lymphoma, or cases of intravascular large B-cell lymphoma or plasmablastic lymphoma that are limited to the skin at presentation.5 In contrast, others9,13 have proposed that PCDLBCL-other should also include cases that meet morphologic and clinical criteria for PCDLBCL-LT, but do not express BCL2. Nonetheless, no clear correlation between prognosis and expression of BCL2 or other immunophenotypic markers has been identified,7,9,10 and even those who recommend separating out BCL2-negative cases as PCDLBCL-other note that patients have a similarly unfavorable prognosis as with PCDLBCL-LT and that they are often treated similarly.13

Primary Cutaneous Follicle Center Lymphoma

Primary cutaneous follicle center lymphoma is the most common primary cutaneous B-cell lymphoma and usually affects older adults, men more commonly than women (median age in the 50s; male to female ratio of 1–2:1).5,6,8,10 Most patients present with lesions on the scalp/forehead or trunk, but other cutaneous sites can be involved, including the leg, and may be multifocal.4,5,9,10 Primary cutaneous follicle center lymphomas often appear as firm, red to plum-colored plaques, nodules, or tumors that enlarge slowly.4,5,10 Extraintracutaneous spread is uncommon (10%).4,10 but usually involves the bone marrow and regional lymph nodes. Most patients have an excellent prognosis with more than 95% of patients surviving at 5 years, even if lesions are multifocal or recurrent.4,10 Importantly, the number of centroblasts does not affect prognosis, and, unlike nodal follicular lymphomas, PCFCLs are not graded.6 In addition, the growth pattern (follicular and/or diffuse) does not affect the prognosis.10 Interestingly, PCFCLs involving the leg tend to have a worse outcome6,10 and are more likely to express BCL2, MUM-1, FOX-P1, and IgM.10,14

Primary cutaneous follicle center lymphoma is composed of dermal infiltrates of follicle center cells, including centrocytes and centroblasts, without epidermal involvement. Centrocytes are characterized by irregular, twisted, or cleaved nuclei and, in occasional cases, they may take on a marked spindled morphology (Figure 2, A and B).6 In contrast, centroblasts are large, usually round cells, with open chromatin and 1 to 3 peripheral nucleoli.6 Primary cutaneous follicle center lymphomas may show a follicular, follicular and diffuse, or diffuse growth pattern. Like nodal follicular lymphoma, follicles are morphologically abnormal. They form irregular shapes and lack polarization, tingible body macrophages, and normal mantle zones.6 They are often associated with a prominent stromal component (Figure 2, B).5,10 Notably, reactive T cells are often prominent.10 While this feature is helpful in distinguishing PCFCL from PCDLBCL-LT, it can be misleading, as a mixture of B and T cells can also denote a reactive process.

Advanced tumors may show a predominance of large centrocytes, which can be difficult to distinguish from centroblasts.5 Furthermore, they are less likely to have associated reactive T cells and more likely to have a diffuse growth pattern.6 These cases can be hard to distinguish from PCDLBCL-LT, but usually have remnants of follicular dendritic networks detectable by immunohistochemistry, and also frequently show a different immunohistochemical profile from PCDLBCL-LT (see below). However, if diffuse sheets of centroblasts and immunoblasts are identified in a process limited to the skin at presentation, these lymphomas should be classified as PCDLBCL-LT.6

In addition to pan B-cell markers (CD19, CD20, CD22, CD79a, PAX-5), PCFCLs express BCL6 and less commonly, CD10.10 Distorted follicular dendritic networks may be highlighted by CD21, CD23, or CD35.5,10 Notably, reactive T cells are often prominent.10,14 Expression of CD10 and BCL2 is suggestive of cutaneous involvement by a systemic follicular lymphoma.5,10 As in nodal follicular lymphoma, coexpression of BCL6 and BCL2 is abnormal and indicates a neoplastic process.

The distinction between PCFCL and PCDLBCL-LT has important treatment implications in addition to prognostic implications. Single, small lesions of PCFCL may be treated with surgical excision alone, while larger or multiple localized lesions can be treated with surgical excision and localized radiation therapy.13 Multifocal lesions can be managed expectantly, with radiation to symptomatic lesions, or with systemic rituximab.13 Importantly, unlike PCDLBCL-LT, systemic anthracycline-based chemotherapy (ie, R-CHOP) is not recommended for most patients with PCFCL, even those with relapsed disease.5,10

Diffuse Large B-Cell Lymphoma, Not Otherwise Specified

Diffuse large B-cell lymphoma, not otherwise specified (DLBCL-NOS) is the most common B-cell lymphoma15 and likely represents a heterogeneous group of lymphomas.6 In some cases, it arises from an underlying low-grade B-cell lymphoma, such as nodal follicular lymphoma, but it may also present de novo. Most patients are in their 7th decade
Figure 2. Primary cutaneous follicle center lymphoma. A scalp biopsy sample displays a dense, dermal lymphoid infiltrate with a focally nodular growth pattern (A). Higher magnification of the nodular area reveals a proliferation of spindled centrocytes, as well as intermixed centroblasts and a prominent stromal component (B) (hematoxylin-eosin, original magnifications ×40 [A] and ×200 [B]).

Figure 3. Epstein-Barr virus–positive diffuse large B-cell lymphoma of the elderly. A large area of necrosis (top) is bounded by a dense, atypical lymphoid infiltrate (A). On closer examination, the atypical lymphoid cells include a heterogeneous mixture of enlarged lymphocytes, centroblasts, immunoblasts, and Hodgkin/Reed-Sternberg–like cells (B) (hematoxylin-eosin, original magnifications ×200 [A] and ×600 [B]).

Figure 4. Lymphomatoid granulomatosis, grade 3. A skin biopsy specimen shows extensive ulceration and necrosis (A). Other areas reveal aggregated large B cells with background histiocytes, angioinvasion, and angiodestruction (B) (hematoxylin-eosin, original magnifications ×100 [A] and ×400 [B]).
of life, and men are affected slightly more often than women.\textsuperscript{15} While most patients present with nodal disease, extranodal presentations are not uncommon.\textsuperscript{6,15} In addition, a single region is frequently involved at presentation.\textsuperscript{19} Moreover, these lymphomas are composed of sheets of large B cells, including centroblasts and immunoblasts. However, when a large B-cell lymphoma is limited to the skin at presentation, the current WHO–EORTC classification for cutaneous lymphomas groups these cases as one of the primary cutaneous lymphomas.\textsuperscript{5} Thus, appropriate clinical staging is required to distinguish DLBCL–NOS from PCDLBCL.

**Epstein-Barr Virus–Positive Diffuse Large B-Cell Lymphoma of the Elderly**

Epstein-Barr virus (EBV)–positive DLBCL of the elderly is a recently described EBV–associated lymphoma.\textsuperscript{16,17} It affects patients older than 50 years who do not have a known immunodeficiency and do not meet criteria for other EBV–associated processes or lymphomas (such as infectious mononucleosis, lymphomatoid granulomatosis, and plasmablastic lymphoma).\textsuperscript{16–18} Most patients are men (male to female ratio of at least 2:1) with a median age of 71.\textsuperscript{17,18} In addition, this lymphoma increases in frequency with age, making up the highest proportion of DLBCLs in persons older than 90 years.\textsuperscript{17,18} It is thought to be related to deterioration of the immune system with age.\textsuperscript{16–18} Extranodal disease is common (70%) and may be the only site of disease at presentation (20%).\textsuperscript{17,18} Furthermore, the skin is the most common extranodal site involved.\textsuperscript{16–18} The disease follows an aggressive course and median patient survival is 2 years.\textsuperscript{17,18}

Epstein-Barr virus–positive DLBCL of the elderly shows variable morphologic findings, even within a single biopsy specimen.\textsuperscript{16–18} Often, there is a polymorphous mixture of atypical B cells, including centroblasts, immunoblasts, and cells that resemble Hodgkin/Reed-Sternberg cells (Figure 3, A and B).\textsuperscript{16–18} In some cases, however, centroblasts and immunoblasts predominate,\textsuperscript{16} and these cases can resemble PCDLBCL–LT. Necrosis is common, and a background mixed inflammatory infiltrate may be seen that includes histiocytes and plasma cells (Figure 3, A and B).\textsuperscript{16–18}

Unlike PCDLBCL–LT, EBV-positive DLBCL of the elderly is, by definition, EBV positive. In addition, it uncommonly expresses BCL6 and frequently expresses CD30.\textsuperscript{6,17,18} EBV–positive DLBCL of the elderly will express at least some B-cell markers (CD19, CD20, CD22, CD79a, PAX-5), as well as IRF4/MUM-1.\textsuperscript{5,17,18}

**Lymphomatoid Granulomatosis**

Lymphomatoid granulomatosis (LyG) is an EBV–driven lymphoproliferative disorder that typically affects adults with a known immunodeficiency, such as human immunodeficiency virus (HIV), iatrogenic immunosuppression, and Wiskott–Aldrich syndrome.\textsuperscript{6,18} Patients are more commonly men (male to female ratio of at least 2:1), and often have widespread disease.\textsuperscript{19,20} Cutaneous involvement is seen in 25% to 50% of patients, but is usually not seen in isolation.\textsuperscript{19,20} Most patients will also have pulmonary involvement (>90%), and central nervous system involvement is common.\textsuperscript{6,19,20} Because of lung involvement, most patients present with respiratory symptoms.\textsuperscript{19,20} In addition, fever, malaise, weight loss, and neurologic symptoms may be seen.\textsuperscript{5,19,20} Cutaneous lesions are diverse. Most often, they are found as tan to plum-colored nodules that may be ulcerated.\textsuperscript{20} Patients also present with papules and/or plaques.\textsuperscript{20} Additionally, disseminated lesions are more common than localized lesions.\textsuperscript{20} Most patients have a poor prognosis with a median survival of 2 years; however, a waxing and waning course or even spontaneous remissions may be seen.\textsuperscript{5,19,20}

Morphologically, LyG is characterized by angiocentric and angiodestructive, large, EBV–positive B cells, often with a mixed background of small lymphocytes, plasma cells, and histiocytes (Figure 4, A and B). Necrosis is common. In skin biopsies, periadnexal involvement is usual.\textsuperscript{20} In addition, a lymphohistiocytic panniculitis with fat necrosis is frequently seen.\textsuperscript{20} The number of EBV–positive B cells forms the basis for separating LyG into 3 histologic grades: (1) no to rare large B cells with fewer than 5 EBV–positive cells per high-power field (HPF), (2) few large B cells with from 5 to 20 EBV–positive B cells per HPF, and (3) numerous large B cells, including aggregates, and greater than 50 EBV–positive B cells per HPF.\textsuperscript{4} Diffuse sheets of large B cells should not be seen in LyG, but instead indicate a DLBCL.\textsuperscript{2} Notably, the number of atypical B cells and EBV–positive cells may vary among different sites/biopsies in the same patient,\textsuperscript{19,20} and more than 1 biopsy may be needed for appropriate grading.\textsuperscript{19} Interestingly, EBV positivity is less frequently identified in cutaneous lesions, possibly reflecting small sample size.\textsuperscript{20} Nonetheless, EBV–positive cells are more likely to be found in grade 3 lesions that mimic PCDLBCL–LT.\textsuperscript{20} In summary, small cutaneous biopsy specimens showing aggregates of large B cells in LyG (ie, grade 3) can mimic PCDLBCL–LT; however, the clinical history of an extensive process in an immunodeficient patient, the angioinvasion and angiodestruction, the mixed background inflammation, and the EBV positivity help to distinguish LyG from PCDLBCL–LT.

**Other Considerations**

Systemic plasmablastic lymphoma may involve the skin and may morphologically resemble PCDLBCL–LT. However, unlike PCDLBCL–LT, it typically occurs in immunodeficient patients, especially HIV–positive men, and presents with extensive systemic disease.\textsuperscript{6} Further, this lymphoma often lacks CD20 and PAX5, and is often EBV positive.

Iatrogenic immunodeficiency–associated lymphoproliferative disorders are defined in the 2008 WHO classification as lymphoid proliferations or lymphomas that arise in patients treated with immunosuppressive medications for reasons other than transplant, usually for autoimmune diseases.\textsuperscript{6} These disorders are often seen after methotrexate and tumor necrosis factor α inhibitor therapy. They include DLBCL and may involve the skin (Figure 5). These cases may express EBV and, importantly, a subset will show partial to complete regression of the lymphoma after withdrawal of the immunosuppressive drug.

EBV–associated mucocutaneous ulcer (EBV MCU) is a newly identified EBV–positive lymphoproliferative disorder that typically affects older adults with known or suspected immunodeficiency.\textsuperscript{21} Most patients are thought to have age-related immunosenescence, but a subset of patients have iatrogenic immunodeficiency.\textsuperscript{21} These patients present with mucosal or cutaneous ulcers that include immunoblasts and Hodgkin/Reed-Sternberg–like cells, often in a mixed inflammatory background of lymphocytes, plasma cells, histiocytes, and eosinophils.\textsuperscript{22} While the large B cells may raise the possibility of PCDLBCL–LT, the mixed inflammatory background would be unusual in PCDLBCL–LT. In
addition, the immunophenotypes of the 2 entities differ. In EBVMCU, the large B cells are EBV positive and CD30+, sometimes express CD15, and may lack expression of CD20.\(^{21}\) BCL6 expression is uncommon.\(^{21}\) Importantly, patients with EBVMCU show a spontaneously remitting or waxing and waning clinical course.\(^{21}\)

**CONCLUSION**

PCDLBCL-LT is a recently recognized DLBCL that presents with skin-confined disease, often on the leg(s) of an elderly woman. It is composed of diffuse, monotonous sheets of centroblasts and immunoblasts and typically expresses BCL2, IRF4/MUM1, FOXP1, BCL6, and IgM. While a variety of primary cutaneous and systemic/extracutaneous lymphomas may show similar features, the combination of clinical findings, morphology, and immunophenotype helps to distinguish this lymphoma from other diagnostic considerations, with both important prognostic and treatment implications for patients.

**References**