Recent advances in the classification, diagnosis, and prognosis of the three major entities of primary cutaneous B-cell lymphoma have contributed to a better understanding and management of this disease.

Primary Cutaneous B-Cell Lymphomas: Recent Advances in Diagnosis and Management
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Background: Primary cutaneous B-cell lymphoma (PCBCL) is a heterogeneous group of rare clonal B-cell lymphoproliferative disorders with distinct clinicopathologic features from more common nodal B-cell lymphomas.

Methods: We performed a systematic review of the relevant literature in the MEDLINE database and analyzed laboratory and clinical data. This review discusses the three most common types of PCBCL: primary cutaneous marginal zone lymphoma (PCMZL), primary cutaneous follicle-center lymphoma (PCFCL), and primary cutaneous diffuse large B-cell lymphoma, leg type (PCDLBCL, LT).

Results: Skin biopsies with histology, immunohistochemistry, and molecular clonality studies are essential for a correct diagnosis of cutaneous B-cell lymphoma. Comprehensive lymphoma staging with laboratory and imaging studies and bone marrow aspiration and biopsy are important for determining the prognosis and differentiation of PCBCL from secondary skin involvement with systemic B-cell lymphomas. PCMZL and PCFCL are low-grade PCBCLs, with an estimated 5-year disease-specific survival rate of greater than 95%. Surgical excision or focal radiation therapy is sufficient to control stages T1 and T2 disease. Rituximab monotherapy is frequently used for patients with stage T3 disease. PCDLBC, LT is an intermediate-grade B-cell lymphoma, with a 5-year disease-specific survival rate of approximately 50%. An anthracycline-based chemotherapy regimen with rituximab is usually required as initial therapy to improve outcomes.

Conclusions: In less than a decade, significant progress has been made in our understanding of PCBCL. Novel classification, staging, and prognostic systems have resulted in more accurate diagnosis and prognosis. Although no randomized prospective studies have been conducted in PCBCL, therapies derived from systemic B-cell lymphomas have shown promising results.

Introduction
Primary cutaneous B-cell lymphoma (PCBCL) belongs to a group of rare B-cell lymphoproliferative disorders that present in the skin and have no evidence of extracutaneous manifestation at the time of initial diagnosis. Clinicopathologic features of PCBCL are distinct from those of its nodal counterparts. Recently, several advances in the classification, diagnosis, and prognosis of PCBCL have been made.

In 2005, the World Health Organization (WHO) and the European Organization for Research and Treatment of Cancer (EORTC) introduced a new consensus clas-
classification for cutaneous lymphoma, which reconciled previous disagreements between these two classification systems.\(^2,^4\) The WHO classification of lymphomas published in 2001\(^6\) defined PCBCL disease entities based only on histology and molecular parameters, whereas the EORTC classification\(^3\) included both histology and skin site.

Three major disease entities of PCBCL have been recognized in this new joint classification system: primary cutaneous marginal zone lymphoma (PCMZL), primary cutaneous follicle-center lymphoma (PCFCL), and primary cutaneous diffuse large B-cell lymphoma, leg type (PCDLBCL, LT).\(^2\)

The Ann Arbor staging system used for staging of systemic non-Hodgkin lymphoma (NHL) has only limited prognostic value in PCBCL as patients are classified in only two stages: IE and IVE. The International Society for Cutaneous Lymphoma and the Cutaneous Task Force of EORTC (ISCL/EORTC) developed a proposal of a new TNM classification for primary cutaneous lymphomas other than mycosis fungoides and Sézary syndrome.\(^5\) This system is based on the number, size, and area of distribution of tumor lesions (Table). Although several retrospective studies investigated a validity of new classification and staging systems on independent cohorts of patients, no larger prospective study for patients with PCBCL has been conducted to validate these systems in clinical practice.

Two prognostic systems also have been proposed for PCBCL.\(^6,^7\) The National Comprehensive Cancer Network (NCCN) guidelines for NHL recognized differences in the diagnosis and management of PCBCL and created separate recommendations for this group of B-cell malignancies.\(^8\) Herein, we discuss the clinical and pathological characteristics of the most common entities in the group of PCBCL.

### Epidemiology

Primary B-cell lymphoma comprises approximately 20% of all primary cutaneous lymphomas and less than 1% of all NHLs.\(^9\) This disease ranks second among extranodal NHLs, after primary gastrointestinal NHLs.

Smith at al\(^1\) analyzed data from the Surveillance, Epidemiology, and End Results (SEER) registry collected between 1973 and 2001. The age-adjusted incidence rate of PCBCL was 3.9 per million population. This study also suggested that the incidence rates steadily increase with age at diagnosis from 0.09 per million in patients < 30 years old to 10.8 per million in patients ≥ 80 years old (120-fold increase; \(P < .001\)). The male-to-female ratio was 1.4:1 for the entire PCBCL group. Low-grade PCBCLs (PCMZL, PCFCL) usually manifest in middle-age populations, with a median age of 53 and 58 years, respectively.\(^10\) PCDLBCL, LT is a disease of elderly persons, with a median age > 70 years. The male-to-female ratio was 1.4 and 2.1 for PCMZL and PCFCL, respectively, and 0.5 for PCDLBCL, LT.\(^10\) No significant geographic or ethnic differences in the occurrence of PCBCL were reported in the reviewed literature.

### Etiology

Although the etiology of PCBCL is not well understood, several reports from Europe revealed an association between PCMZL with *Borrelia burgdorferi* (Bb).\(^11-13\) Jelić et al\(^12\) reported that 12 of 22 patients (55%) with PCBCL had a positive serology for Bb. Goodlad et al\(^13\) detected Bb-specific DNA sequences in 7 of 20 patients with PCBCL (5 PCMZL, 5 PCFCL, and 2 PCDLBCL, LT). A limited number of cases of PCBCL positive for Bb were treated with antibiotics and showed resolution of lesions.\(^14,^15\) However, three studies that included patients from Europe did not confirm this hypothesis. Takino et al\(^16\) analyzed 60 cases of PCMZL from East Asia, Germany, and the United States using multiple clinicopathologic characteristics. All 60 cases were

### Table. — ISCL/EORTC Proposal on TNM Classification of Cutaneous Lymphoma Other Than Mycosis Fungoides and Sézary Syndrome

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<tr>
<td>T1</td>
<td>Solitary skin involvement</td>
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<tr>
<td>T1a</td>
<td>A solitary lesion &lt; 5-cm diameter</td>
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<tr>
<td>T1b</td>
<td>A solitary &gt; 5-cm diameter</td>
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<tr>
<td>T2</td>
<td>Regional skin involvement multiple lesions limited to 1 body region or 2 contiguous body regions</td>
</tr>
<tr>
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<td>All-disease-encompassing in a &lt; 15-cm diameter circular area</td>
</tr>
<tr>
<td>T2b</td>
<td>All-disease-encompassing in a &gt; 15- and &lt; 30-cm diameter circular area</td>
</tr>
<tr>
<td>T2c</td>
<td>All-disease-encompassing in a 30-cm diameter circular area</td>
</tr>
<tr>
<td>T3</td>
<td>Generalized skin involvement</td>
</tr>
<tr>
<td>T3a</td>
<td>Multiple lesions involving 2 noncontiguous body regions</td>
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<td>T3b</td>
<td>Multiple lesions involving ≥ 3 body regions</td>
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<td>No clinical or pathologic lymph node involvement</td>
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<tr>
<td>N1</td>
<td>Involvement of 1 peripheral lymph node region that drains an area of current or prior skin involvement</td>
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<tr>
<td>N2</td>
<td>Involvement of 2 or more peripheral lymph node regions or involvement of any lymph node region that does not drain an area of current or prior skin involvement</td>
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<td>N3</td>
<td>Involvement of central lymph nodes</td>
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<td>No evidence of extracutaneous non-lymph node disease</td>
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<td>M1</td>
<td>Extracutaneous non-lymph node disease present</td>
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negative for Bb DNA or for API2-MALT1 fusion. Goteri et al. \textsuperscript{17} tested 73 paraffin-embedded tissue samples from patients with PCBCL using polymerase chain reaction (PCR) and showed no evidence of the presence of Bb-specific sequences. Schöllkopf et al. \textsuperscript{18} analyzed 3,055 patients with NHL and 3,187 controls in a Danish-Swedish case-controlled study. A positive history of a tick bite or antibodies against \textit{Borrelia} infection in serum was found in 1,579 patients and 1,358 controls. Statistical analysis suggested that the overall risk of NHL was not associated with a self-reported history of tick bite or the presence of anti-\textit{Borrelia} antibodies. Interestingly, in analyses of NHL subtypes, both parameters were associated with an increased risk of mantle cell lymphoma.

### Molecular Biology

Recent progress in molecular biology and increased research interest in the pathobiology of cutaneous lymphoma have resulted in new findings, with potential clinical implications.

Dijkman et al. \textsuperscript{19} employed array-based comparative genomic hybridization, fluorescence in situ hybridization, and examination of promoter hypermethylation in patients with PCFCL (n = 19) and PCDLBCL, LT (n = 12). In patients with PCFCL, the most frequent recurrent aberrations were DNA amplifications at 2p16.1 (63%) and deletion of chromosome 14q32.33 (68%). In patients with PCDLBCL, LT, the most prominent alterations were a high-level DNA amplification of 18q21.31-q21.33 (67%) and deletions of a small region within 9p21.3 containing the CDKN2A and CDKN2B genes. Homozygous deletion of 9p21.3 was detected in 5 of 12 patients (42%) with PCDLBCL, LT but in none of 19 patients with PCFCL. Complete methylation of the promoter region of the CDKN2A gene was demonstrated in 2 patients with PCDLBCL, LT but not in patients with PCFCL. All patients with PCDLBCL, LT with deletion of 9p21.3 and/or complete methylation of CDKN2A died as a result of lymphoma.

Bhagavathi et al. \textsuperscript{20} evaluated 10 patients with PCBCL using immunohistochemistry (IHC) and detected activation of nuclear factor kappa B (NFkB) pathway in 70% of patients. Only 1 patient showed Epstein-Barr virus (EBV) positivity using EBV-encoded RNA (EBER) staining, suggesting that a different mechanism (or mechanisms) may be responsible for activation of this pathway.

A study by van Maldegem et al. \textsuperscript{21} reported that the majority of PCMZls expressed immunoglobulin G (IgG), IgA, and IgE and did not show Ig-variable heavy/light chain (IgVH/IgVL) gene repertoire restriction, as frequently seen in other extranodal MZL. Furthermore, the isotype-switched PCMZls lacked a receptor for interferon gamma-induced chemokines (CXCR3), suggesting that PCMZL evolved in a different inflammatory environment than did noncutaneous extranodal MZL.

Perez et al. \textsuperscript{22} analyzed the nucleotide sequences of clonal IgVH gene rearrangement in 51 patients with PCBCL (PCFCL = 25, PCMZL = 19, and PCDLBCL, LT = 7). The authors showed that all but 1 patient with PCBCL revealed extensive somatic hypermutations. The mutational pattern suggested a possibility of antigenic selection with putative common antigen epitopes.

Dijkman et al. \textsuperscript{23} reported that a significant proportion of patients with PCFCL and PCDLBCL, LT demonstrated aberrant somatic hypermutations of BCL-6, MYC, RhoH/TTF, and PAX5 genes. Interestingly, the higher expression of activation-induced cytidine deaminase (AID) was detected in patients with PCDLBCL, LT than in those with PCFCL. This enzyme creates somatic mutations responsible not only for antibody diversity but also for lymphomagenesis. \textsuperscript{24}

### Primary Cutaneous B-Cell Lymphoma

#### Prognostic Scoring Systems

Smith et al. \textsuperscript{7} analyzed 926 patients in the SEER registry and created a new cutaneous B-cell lymphoma prognostic index (CBCL-PI) based on histology type and skin site. Four prognostic index groups were identified: (1) group IA: indolent histology involving any skin site, (2) group IB: diffuse large B-cell histology involving favorable skin sites (head/neck, arm), (3) group II: diffuse large B-cell histology involving unfavorable sites (trunk, legs, disseminated), and (4) group III: immunoblastic large B-cell histology involving unfavorable sites. The prognostic groups had 5-year relative survival rates of 94%, 86%, 60%, and 34%, respectively.

The International Extranodal Lymphoma Study Group (IELSG 11) proposed a new prognostic index for indolent cutaneous B-cell lymphoma: CLIPI. \textsuperscript{6} This prognostic scoring system is based on three prognostic factors: elevated serum lactate dehydrogenase (LDH) level (> upper limit of normal), morphology of the lesion (nodule vs other), and number of lesions (> 2). These factors were independent predictors for progression-free survival (PFS). After each prognostic factor was assigned a value of 1, patients were stratified to the following three risk groups with a score of 0 to 3: low risk = 0, intermediate risk = 1, and high risk = 2 and 3. The 5-year PFS rates were 91%, 64%, and 48%, respectively (P < .001).

#### Diagnosis

Punch (4–6 mm), wedge-incisional, or excisional biopsies are most frequently performed for the diagnosis of PCBCL. IHC with a panel of antibodies against B-cell antigens including CD20, CD79a, CD5, CD10, BCL-2, BCL-6, kappa/lambda, and MUM1/IRF4 is an essential diagnostic tool. Ig heavy-chain and light chain gene rearrangement by PCR can be done on paraffin-embedded tissue to confirm a clonal origin of B cells. Flow cytometry on the fresh tissue can also be useful if the biopsy specimen contains a sufficient number of malignant cells.
**Staging**

Staging studies for patients with PCBCL are important not only for the determination of prognosis but also for the confirmation of diagnosis, as neither histology nor IHC can differentiate with absolute certainty PCBCL from cutaneous involvement with systemic B-cell lymphomas. According to ISCL/EORTC recommendations for staging evaluation (Table) of cutaneous lymphomas other than mycosis fungoides and Sézary syndrome, patients should undergo the following testing: a complete history and physical examination, complete blood cell count with differential count (CBC/Diff), chemistry with LDH, flow cytometry on peripheral blood, and imaging with computed tomography (CT) scan of the chest, abdomen, and pelvis with contrast or positron emission-tomography/CT (PET/CT). Although a CT scan is sufficient for a diagnosis of adenopathy and organomegaly, smaller skin lesions can be missed. Fusion PET/CT on the other side can visualize metabolically active disease in relatively small lesions, which might sometimes be missed on physical examination.

Bone marrow aspiration and biopsy (BMAB) is recommended for all patients with intermediate-grade PCBCL. However, there is not a consensus on bone marrow testing in patients with indolent PCBCL.

Quereux et al. retrospectively analyzed 62 patients with PCBCL who underwent staging BMAB. After exclusion of 4 patients with adenopathy and 1 patient with pancytopenia, a positive bone marrow was found in only 3 of 57 patients (5%), suggesting that a routine BMAB might not be necessary.

Senff et al. analyzed results of BMAB in 275 patients with indolent B-cell lymphomas (82 with MZL and 193 with follicular lymphoma [FCL]) who presented with skin lesions. In the group with MZL, 2 of the 82 patients (2%) presented with bone marrow involvement, which was only an extracutaneous manifestation of lymphoma. In the FCL group, 22 of the 193 patients (11%) had bone marrow involvement; in 9 of these patients, the bone marrow was the only extracutaneous disease. Patients with FCL plus skin lesions and bone marrow involvement had a significantly worse prognosis than did patients with skin lesions only (5-year disease-specific survival rate of 63% vs 95%). These results demonstrated that staging studies with bone marrow testing are important in patients with FCL but have limited value in patients with MZL manifesting with skin lesions. The NCCN guidelines for NHL consider BMAB to be optional for patients with PCMLZ.

**Therapy**

The choice of therapy for PCBCL is usually based on histology (low grade vs intermediate grade), anatomic location, size, and number of tumor lesions. As a rule, low-grade (indolent) PCBCL can be managed with observation or skin-directed therapies (surgical excision, radiation therapy), whereas intermediate-grade PCBCL requires systemic therapy with involved-field radiation therapy (Fig 1).

**Rituximab Monotherapy**

**Systemic:** Rituximab monotherapy has been successfully used in systemic low-grade B-cell malignancies. Because PCBCL expresses CD20 antigen, several small pilot studies with rituximab monotherapy were conducted in patients with PCBCL. Fenot et al. reported the results of a retrospective study with single-agent rituximab in 8 patients with PCDLBCL, LT. Objective responses were observed in 75% of patients after 4 weekly courses of rituximab. However, all patients relapsed, with a median disease-free survival of 5.3 months and a median follow-up 17.7 months.

Valencak et al. observed a high complete response (CR) rate of 87.5% in patients with low-grade PCBCL (11 PCFCL and 5 PCMLZ) with 4 to 6 weeks of rituximab monotherapy. Two patients achieved a partial response (PR). Of 14 patients, 5 (35%) with a CR relapsed within 6 to 37 months.

Morales et al. reported on a retrospective study of 15 patients with indolent PCBCL (10 PCFCL, 5 PCMZL) treated with rituximab induction therapy followed by variable maintenance therapy in a subset of patients. The objective response rate was 87%, with 60% CRs and 27% PRs. All patients with PCFCL showed a response, with 80% being a CR. Of 5 patients with PCMZL, 3 (60%) had a response, with a median follow-up of 36 months. The median duration of response was 24 months.

**Intralesional:** Treatment with intralesional rituximab was tested in a limited number of patients. Kyrtsonis et al. reported that 2 patients with multiple lesions of PCMZL treated with intralesional rituximab for 18 consecutive weeks achieved regression of lesions. Heinzerling et al. treated 2 patients with PCBCL with intralesional rituximab, achieving partial regression of the lesions. Patients in both studies did not experience any adverse reactions except pain at the injection site.

Kerl et al. reported on 8 patients with low-grade PCBCL treated with rituximab. Six patients received intralesional rituximab, 10 mg to 30 mg per lesion, 3 times weekly for 1 or 2 cycles at 4-week intervals. Two patients received intravenous (IV) rituximab, 375 mg/m² once weekly for 4 consecutive weeks. The overall response rate was 100%. Two patients treated with IV rituximab did not relapse during a follow-up period of 18 to 24 months. Four patients treated intralesionally relapsed, with new lesions within a mean of 6 months after treatment. The injected lesions did not recur.

Roguedas et al. treated PCFCL patients with intralesional rituximab and observed regression of both injected and noninjected lesions. Because only a limited number of patients have been treated with intralesional rituximab so far, larger prospective studies are necessary to confirm the safety and efficacy of this approach.
**Intralesional Interferon:** A small number of patients with PCMZL and PCFCL were treated with intralesional interferon alpha (IFN-α), with doses ranging from 1 to 6 million IU given 3 times a week. Interestingly, all patients achieved a CR, with a local recurrence rate of approximately 25%.

In a phase II study of intralesional adenovirus IFN-γ, Dummer et al\(^{34}\) treated patients with cutaneous T-cell and B-cell lymphomas, with a good tolerance and responses in about 50% of patients. Distant responses in noninjected lesions were observed in about one-third of patients. This study suggested that activation of the immune system with biologic agents could be employed as a therapy for PCBCL.

**Radioimmunotherapy:** Radioimmunotherapy (RIT) has become an important part of the therapeutic armamentarium of systemic recurrent low-grade B-cell lymphomas. Maza et al\(^{35}\) conducted a pilot study using RIT with yttrium-90 (\(^{90}\)Y)-ibritumomab tiuxetan in patients with PCBCL. Ten patients with relapsed PCBCL (PCFCL and PCDLBCL, LT) were treated with rituximab on days 1 and 8 followed by a single dose of \(^{90}\)Y-ibritumomab tiuxetan. The CR rate was 100%, with a median time to relapse of 12 months. These data suggest that RIT could be an effective therapeutic option for patients with PCBCL.

**External-Beam Radiation Therapy:** Senff et al\(^{36}\) reported on the results of radiotherapy with curative intent in 153 patients with PCBCL classified according to the WHO-EORTC classification in a multicenter, retrospective study. This large cohort of PCBCL patients included 25 cases with PCMZL, 101 with PCFCL, and 27 with PCDLBCL, LT. The median radiation dose was 40 Gy (range, 20 Gy to 46 Gy). Complete remission was achieved in 151 of 153 patients (99%). Relapse rates for patients with PCMZL, PCFCL, and PCDLBCL, LT were 60%, 29%, and 64%, respectively, and the overall 5-year disease-specific survival rates were 95%, 97%, and 59%. Patients manifesting PCFCL on their legs had a higher relapse rate (63%) and a worse disease-specific survival rate (44%) than did patients with PCFCL on other sites (relapse rate 25%; disease-specific survival rate 99%). This study suggested that radiation therapy is an effective treatment for patients with PCBCL; however, patients with PCDLBCL, LT and PCFCL manifesting on the legs require more aggressive systemic therapy.

Neelis et al\(^{37}\) reported on the results of low-dose palliative radiotherapy (4 Gy in 2 fractions) in patients...
with PCBCL, which included 18 patients with low-grade disease (10 PCMZL and 8 PCFCL) with 44 symptomatic plaques and tumors. A CR was observed in 33 lesions (75%) at the first follow-up visit (4 to 6 weeks following radiation therapy). A PR was seen in 5 lesions (11%), and stable disease was seen in 6 patients (13%). The overall response rate (CR and PR) was 86%. After a median of 6.3 months, 13 of 44 lesions were re-treated at the same site due to persistent (n = 8) or recurrent (n = 5) symptomatic disease, using a conventional-dose fractionation regimen with 20 Gy in 8 fractions. These results demonstrated that a short radiotherapy regimen with a low total dose was efficacious, with acceptable toxicity.

**Combined Chemotherapy:** Senff et al. reported cumulative data from 8 publications on 104 PCFCL patients with disseminated cutaneous lesions using systemic chemotherapy. The CR rate was 85%, with a relapse rate of 48%. A majority of patients received a regimen of cyclophosphamide, doxorubicin, vincristine, prednisone (CHOP) or CHOP-like chemotherapy. A review of the literature suggested that patients with PCDLBCL, LT treated with CHOP (n = 29) or cyclophosphamide, vincristine, and prednisone (n = 3) had a CR rate of 81%. Of 26 patients, 14 (54%) relapsed.9

Grange et al. compared the outcomes of patients treated with different anthracycline-containing chemotherapy regimens and rituximab (12 patients) with those of patients treated with other therapies (48 patients). The 2-year survival rates were 81% and 59%, respectively. Eleven of 12 patients (92%) achieved a CR vs 62% of the group treated with other therapies. Although limited published data are available on the use of CHOP with rituximab in PCDLBCL, LT, this regimen is frequently used in clinical practice based on data extrapolated from clinical studies conducted in systemic diffuse large B-cell lymphoma.

**Primary Cutaneous Marginal Zone Lymphoma**

PCMZL is included in the group of extranodal marginal zone lymphomas of the mucosa-associated lymphoid tissue type in the 2008 WHO classification and accounts for approximately 25% of all PCBCLs.2 Patients usually present with red or violaceous papular or nodular lesions on the trunk or arms. A majority of patients present with multiple lesions.2-39

**Histopathology**

The morphology of cutaneous lesions (Fig 2) shows a nodular or diffuse infiltrate of mixed population of small- to medium-sized lymphocytes, marginal zone B cells, lymphoplasmacytoid cells, and plasma cells with a few centroblast or immunoblast-like cells. PCMZLs infiltrate the dermis, with no propensity for the epidermis.1,2

**Immunophenotype and Genetics**

Malignant cells coexpress CD19, CD20, CD22, CD79a, and BCL-2. The IgV_{H} is rearranged in a majority of patients. Chromosomal abnormalities, including t(14;18) (q32;q21) involving the IgH and MLT genes and t(3;14) (p14;q32) involving the IgH and FOXP1 genes,1,2 were detected only in a small proportion of patients.
Prognosis
The prognosis of patients with PCMZL is excellent, with a 5-year disease-free survival rate of 98% to 100% despite multiple relapses (46%). This lymphoma rarely transforms into large B-cell lymphoma or shows systemic dissemination.

Therapy
Asymptomatic patients with stable solitary or multiple lesions can be observed. The most common initial therapy for a solitary lesion or a small number of lesions (T1, T2) includes complete surgical excision or radiation therapy. Patients with multifocal lesions may respond to rituximab, RIT, or spot external-beam radiation therapy. A small number of patients have been treated with intrallesional rituximab or interferon-α or corticosteroids. Patients with PCMZL usually do not require treatment with systemic chemotherapy except in rare cases where extracutaneous extension or refractory disease to radiation therapy or immunotherapy. Chemotherapy or chemoimmunotherapy indicated for treatment of systemic MZL is usually used in these circumstances.

Primary Cutaneous Follicle-Center Lymphoma
PCFCL is the most common subtype of cutaneous B-cell lymphoma, comprising about 55% of all PCBCLs. Patients usually present with red-brown papules or nodules localized on the scalp, forehead, or trunk.

Histopathology and Immunophenotype
PCFCL lesions can show a nodal, nodal and diffuse, or diffuse pattern consisting of medium to large centrocytes with a variable number of centroblasts (Fig 3) and an absence of epidermotropism. Malignant cells coexpress CD19, CD20, CD22, CD79, and BCL-6. CD10 is usually positive in lesions with a follicular growth pattern but negative in lesions with a diffuse growth pattern. BCL-2 and MUM1/IRF4 expression by IHC is detected in about 10% of patients. In contrast to nodal follicular lymphoma, t(14;18) is usually negative. However, several studies demonstrated the presence of BCL-2 rearrangements in a minority of patients using fluorescence in situ hybridization or PCR.

Prognosis
Patients with PCFCL have an excellent prognosis, with a 5-year disease-specific survival rate of 95% to 98%. The cutaneous relapse rate is approximately 30%, and a number of relapses do not correlate with prognosis. The histologic pattern does not have any impact on long-term outcome. Interestingly, patients presenting with cutaneous lesions on one or both legs showed a significantly worse prognosis compared with patients with lesions manifesting at sites other than the legs (5-year overall survival rate = 22% vs 92%). In a multivariate analysis, only location on the legs and expression of FOXPI were significant prognostic factors associated with a poor prognosis.

Fig 3. — Primary cutaneous follicle-center lymphoma, with a follicular growth pattern. (A) Note the closely packed follicles without mantle zones and an unremarkable overlying epidermis (hematoxylin-eosin, original magnification ×20). (B) Neoplastic follicles are devoid of tingible body macrophages and lack polarity (hematoxylin-eosin, original magnification ×400). (C) Centrocytes predominate, along with few centroblasts and histiocytes (hematoxylin-eosin, original magnification ×600).
Therapy
Treatment of patients with PCFCL follows recommendations for treatment of patients with PCMZL (Fig 1) and includes observation, complete surgical excision, or radiation therapy for a single lesion or small numbers of lesions (stage T1 or T2). Asymptomatic patients with more advanced skin disease can be observed or treated with immunotherapy or RIT. Systemic therapy can be considered in patients manifesting with multiple lesions on the lower extremities, although this recommendation is based only on a retrospective analysis of a small number of patients.9

Primary Cutaneous Diffuse Large B-Cell Lymphoma, Leg Type
PCDLBCL, LT is an intermediate-grade B-cell lymphoma that comprises only 1% to 3% of all cutaneous lymphomas and approximately 10% to 20% of PCBCLs. Skin lesions most frequently resembling tumor nodules can be solitary or multiple, with a predilection to the lower extremities and/or trunk.

Histopathology and Immunophenotype
Morphologically, lesions usually show a diffuse infiltrate of large B cells, centroblasts, or immunoblasts, with frequent invasion into the subcutis (Fig 4). Malignant cells coexpress CD20, CD79a, BCL-2, MUM1/IRF4m, and intracytoplasmic IgM in a majority of cases.1,8,42

Genetics
Clonality studies are usually positive for a clonal IgH gene rearrangement by PCR. A characteristic chromosomal abnormality for nodal low-grade follicular lymphoma with t(14;18)(q32;q21) is not present. The inactivation of CDKN2A by either deletion of 9p21.3 or promoter hypermethylation was found in 67% of patients.43 This molecular abnormality was associated with a worse prognosis. A majority of patients show chromosomal aberrancies, among which gains of 18q and 7p and losses of 6q were most frequent.2

Prognosis
The course of disease is characterized with frequent relapses and dissemination into extracutaneous regions. The 5-year disease-specific survival rates ranged from 43% to 63% in three larger studies.10,38,40 In a multivariate analysis, no independent prognostic factor was found.10 In a retrospective study, patients treated with combined anthracycline and rituximab-based therapies had a more favorable short-term outcome compared to patients treated with chemotherapy regimens without rituximab.38

Therapy
Multiagent chemotherapy with rituximab (R-CHOP) followed by involved-field radiation therapy is a recommended frontline therapeutic approach, according to the NCCN guidelines.8 Patients who are not eligible for systemic chemotherapy may benefit from external-beam radiation therapy or RIT.

Conclusions
The novel WHO-EORTC classification, the TNM staging system, and the prognostic scoring system in PCBCL

Fig 4.—Primary cutaneous diffuse large B-cell lymphoma, leg type. (A) Diffuse infiltrate involves the entire dermis and extends into the subcutaneous fat (hematoxylin-eosin, original magnification ×20). (B–C) Note the predominance of large transformed cells with vesicular chromatin and prominent nucleoli (immunoblasts).
have contributed to a better understanding and management of these rare lymphomas. Although conducting large prospective clinical trials in patients with PCBCL will be difficult due to the rarity of this disease, it is possible that novel targeted therapies developed for more common systemic B-cell lymphomas will also demonstrate efficacy in patients with PCBCL.

References


