Primary Cutaneous Diffuse Large B-Cell Lymphoma, Leg Type

Clinicopathologic Features and Prognostic Analysis in 60 Cases

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Objectives: To describe clinicopathologic features and to identify prognostic factors in a large series of primary cutaneous diffuse large B-cell lymphoma, leg type (PCLBCL LT), as defined in the recent World Health Organization–European Organization for Research and Treatment of Cancer classification of cutaneous lymphomas.

Design: Retrospective multicenter study from the French Study Group on Cutaneous Lymphomas.

Setting: Nineteen departments of dermatology in 10 regions of France.

Patients: Sixty patients with a PCLBCL LT included in the registry of the French Study Group on Cutaneous Lymphomas.

Main Outcome Measures: Age, sex, outcome, therapy, B symptoms, cutaneous extent, number of lesions, location (leg vs nonleg), serum lactate dehydrogenase level, and MUM-1 and Bcl-2 expression were recorded. Disease-specific survival was used as the main end point. Prognostic factors were identified using a Cox proportional hazards model.

Results: Primary cutaneous diffuse large B-cell lymphoma, leg type is characterized by a predilection for the leg (72%), a high proportion of Bcl-2 expression (85%), an advanced age at onset (mean age, 76 years), and frequent relapses and extracutaneous dissemination. The overall 5-year disease-specific survival rate was 41%. Location on the leg and multiple skin lesions were predictive of death in multivariate analysis. Although no variable related to therapy was significantly associated with survival, patients recently treated with combinations of anthracycline-containing chemotherapies and rituximab had a more favorable short-term outcome.

Conclusions: Primary cutaneous diffuse large B-cell lymphoma, leg type is a distinct entity with a poor prognosis, particularly in patients with multiple tumors on the legs. Despite the advanced age of many patients, the prognosis could be improved with combinations of anthracycline-containing chemotherapies and rituximab.

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In 2005, a new World Health Organization–European Organization for Research and Treatment of Cancer (WHO-EORTC) classification of cutaneous lymphomas was proposed and was widely accepted as an important consensual advance for the characterization and management of cutaneous lymphomas. In this classification, primary cutaneous B-cell lymphomas (PCBCLs) were divided into the following 3 main groups: primary cutaneous marginal zone B-cell lymphoma, primary cutaneous follicle center cell lymphoma, and primary cutaneous diffuse large B-cell lymphoma, leg type (PCLBCL LT). Whereas the first 2 groups had been identified long before and studied in numerous large reports, the third group was newly defined and had not yet been characterized by large multicenter studies. Since the report of the WHO-EORTC classification, 2 studies have included information about 40 and 51 cases of PCLBCL LT as subgroup analyses of larger series of PCBCLs of different subtypes. However, no large studies specifically dedicated to PCLBCL LT have been published to date, to our knowledge. In addition, although PCLBCL LT is known to have a more aggressive clinical behavior than other groups of PCBCLs, we are aware of only 1 study that has attempted to identify prognostic factors in these patients. In this study, we analyzed the outcome, therapy, prognostic factors, clinical characteristics, and
immunohistologic features in a large series of patients with PCLBCL LT.

**METHODS**

**PATIENT SELECTION**

A retrospective review of PCBCLs included in the registry of the French Study Group on Cutaneous Lymphomas between January 1, 1988, and March 31, 2006, was carried out. Patients with PCLBCL LT according to the WHO-EORTC classification were selected for analysis after clinicopathologic review.

Primary cutaneous B-cell lymphomas were defined as B-cell lymphomas manifesting on the skin without evidence of extracutaneous disease. Among PCBCLs, PCLBCL LT was defined histologically as cases with a predominance or confluent sheets of centroblasts and immunoblasts, irrespective of the location of skin lesions and Bcl-2 protein expression. There were no recorded patients with associated chronic lymphocytic leukemia or Richter syndrome.

To avoid selection biases, events occurring after diagnosis were not used as exclusion criteria. In particular, patients unable to receive any treatment because of their poor general condition, those who developed extracutaneous dissemination within 6 months after diagnosis, and those who died soon thereafter were included in the study.

**HISTOLOGIC AND IMMUNOHISTOCHEMICAL REVIEW**

All cases were reviewed by a panel of 3 of us (B.V., J.W., and T.P.) who were blinded to the clinical data to confirm the inclusion criteria based on the predominance (≥80%) of centroblasts (large cells with round or oval nuclei and several small nucleoli generally sticking to the nucleus membrane) and immunoblasts (large cells with round nuclei and ≥1 large central nucleoli). Cases showing a large proportion of large centrocytic cells (cleaved cells) were excluded. For each case, hematoxylin-eosin stains and CD20- and CD3-immunostained slides from formalin-fixed and paraffin-embedded biopsy specimens were required. In all cases, tumor cells expressed CD20 and were negative for CD3. The cases that did not correspond to the morphological and phenotypical criteria of centroblastic or immunoblastic B-cell lymphomas were excluded.

Unstained sections or paraffin blocks were subsequently collected from each center to perform Bcl-2 and MUM-1 immunostains. The analysis was performed in the same laboratory (that of T.P.) at the same time to avoid technique-dependent variability using an automated system (BenchMark; Ventana Medical System, Illich, France). We used reactive lymph node specimens as positive and negative controls. The following monoclonal antibodies were used for the study: clone 124 for Bcl-2 protein and clone mum1p for MUM-1 protein (Dako Company, Glostrup, Denmark). After consensus among reviewers, an estimated quantification of the proportion of neoplastic large cells that showed unequivocal Bcl-2 and MUM-1 positivity was given, ranging from 0% to 100%. As in previous studies, Bcl-2 expression was considered positive when this proportion exceeded 50%. MUM-1 expression was categorized as positive (≥50% positive tumor cells), intermediate (30%-49% positive tumor cells), or negative (<30% positive tumor cells).

**CLINICAL AND FOLLOW-UP DATA**

All medical records were reviewed. The following clinical characteristics were recorded at diagnosis and were evaluated for prognostic value: age, sex, B symptoms, number of skin lesions, duration of skin lesions before diagnosis, serum lactate dehydrogenase level, anatomical site (arm, leg, head and neck, anterior aspect of the trunk, or posterior aspect of the trunk), and cutaneous extent (namely, “localized” when 1 or multiple skin lesions were restricted to 1 anatomical site and “disseminated” when several anatomical sites were involved). Follow-up data were recorded until April 1, 2006, including initial and subsequent therapies, achievement of a complete response, cutaneous relapse, extracutaneous progression of the disease, final status, and date and cause of death. Causes of death were ascertained in most cases by physician members of the French Study Group on Cutaneous Lymphomas who followed up patients and in other cases by questioning their general practitioners. Follow-up ranged from 0.3 to 155 months (mean follow-up, 32 months). Fifty-two patients (86.7%) were followed up until death, until the end point, or for longer than 5 years, whereas 8 patients (13.3%) were lost to follow-up after less than 5 years (range, 17-49 months).

**STATISTICAL ANALYSIS**

Disease-specific survival duration was calculated from diagnosis to the date of disease-related death or censoring. Patients whose deaths were unrelated to lymphoma were considered censored.

Prognostic factors were identified by disease-specific survival univariate and multivariate analyses using a Cox proportional hazards model. Factors significant at the 0.2 level in univariate analysis were included in stepwise regression multivariate analyses. Comparisons between subgroups of patients according to factors of prognostic value were performed using χ² test or Fisher exact test for categorical variables and t test or Mann-Whitney test for continuous variables. The Kaplan-Meier method was used to estimate lymphoma-specific survival and to construct corresponding survival curves. Survival rates were compared separately for each category of prognostic variable identified by the Cox proportional hazards model using the Mantel-Cox test.

**BASELINE CLINICAL AND HISTOLOGIC CHARACTERISTICS AND FOLLOW-UP DATA**

Sixty patients met the inclusion criteria. Thirty-two had been included in a previous study. All patients had negative staging investigations at diagnosis, including physical examination (100% of cases), routine laboratory test results (100%), bone marrow cytologic or histologic features (90%), chest radiography or thoracic computed tomography (100%), abdominal ultrasonographic tomography or abdominal computed tomography (100%), and lymph node histologic features in patients with clinically enlarged lymph node (13%).

The main characteristics of patients at diagnosis and the follow-up data are summarized in Table 1. The female-male sex ratio was 1.6. Patient age ranged from 44 to 96 years (mean age, 76 years; median age, 77 years). The performance status was 0 (fully active), 1 (ambulatory), 2 (bedridden <50% of the time), 3 (bedridden 50% of the time), and 4 (completely bedridden) in 12, 13, 4, and 2 patients, respectively, and was unavailable for 25 patients. Fifty-four patients had cutaneous nodules or tumors, 3 patients had deeply infiltrated plaques, 2 patients had large subcutaneous tumors, and 1 patient had a leg ulcer. Twenty
patients (33.3%) had 1 lesion, 19 patients (31.7%) had 2 to 5 lesions, and 21 (35.0%) had more than 5 lesions. Eight patients (13.3%) had lesions on the trunk, 9 patients (15.0%) had lesions on the arm, 11 patients (18.3%) had lesions on the head, and 43 patients (71.7%) had lesions on the leg (in 5 of these 43 patients, lesions were located both on the leg and at other anatomical sites). Using the previous EORTC classification, all 43 of these cases would have been classified by most authors as PCLBCL of the leg, whereas 17 cases without leg lesions (28.3%) would have been classified as primary cutaneous follicle center cell lymphoma. In the present study, these 17 cases are referred to as nonleg PCLBCL LT, as defined in the WHO-EORTC classification.  

Seven patients (11.7%) had a high serum lactate dehydrogenase level, 6 patients (10.0%) had B symptoms, and 2 patients (3.3%) had both conditions. Bcl-2 staining was positive in 51 patients (85.0%). MUM-1 staining was scored as positive, intermediate, and negative in 23 (56.1%), 5 (12.2%), and 13 (31.7%) of 41 patients, respectively, and was unavailable in 19 patients.  

Table 2 summarizes first-line and subsequent therapies administered in our 60 patients. First-line therapy was most often radiation therapy (38.3%) or variable combinations of systemic chemotherapies (49.9%) with or without rituximab. In addition, 17 patients (28.3%) received second-line or third-line therapies. Overall, 39 patients (65.0%) were treated with polychemotherapies as first-line or subsequent therapies during the course of the disease (data not shown). These included 9 patients (15.0%) who received polychemotherapies only without anthracycline, 18 patients (30.0%) who received anthracycline-containing chemotherapies without rituximab, and 12 patients (20.0%) who received various combinations of anthracycline-containing chemotherapies and rituximab. No statistically significant difference with respect to therapies administered was observed between patients with leg vs nonleg PCLBCL LT.

### Table 1. Main Findings at Diagnosis and Follow-up Data and According to Location of Skin Tumors

<table>
<thead>
<tr>
<th>Variable</th>
<th>Total</th>
<th>Leg</th>
<th>Nonleg</th>
<th>P Valueb</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. of cases</td>
<td>60</td>
<td>43</td>
<td>17</td>
<td></td>
</tr>
<tr>
<td>Age, y</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean (range)</td>
<td>76 (44-96)</td>
<td>78 (44-92)</td>
<td>72 (49-96)</td>
<td>.03</td>
</tr>
<tr>
<td>&gt; 75</td>
<td>35 (58.3)</td>
<td>30 (69.8)</td>
<td>5 (29.4)</td>
<td>.004</td>
</tr>
<tr>
<td>Sex</td>
<td></td>
<td></td>
<td></td>
<td>.4</td>
</tr>
<tr>
<td>Male</td>
<td>23 (38.3)</td>
<td>15 (34.9)</td>
<td>8 (47.1)</td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>37 (61.7)</td>
<td>28 (65.1)</td>
<td>9 (52.9)</td>
<td></td>
</tr>
<tr>
<td>No. of lesions</td>
<td></td>
<td></td>
<td></td>
<td>&lt;.001</td>
</tr>
<tr>
<td>1</td>
<td>20 (33.3)</td>
<td>8 (18.6)</td>
<td>12 (70.6)</td>
<td></td>
</tr>
<tr>
<td>&gt; 1</td>
<td>40 (66.7)</td>
<td>35 (81.4)</td>
<td>5 (29.4)</td>
<td></td>
</tr>
<tr>
<td>Extent</td>
<td></td>
<td></td>
<td></td>
<td>.15</td>
</tr>
<tr>
<td>Localized</td>
<td>48 (80.0)</td>
<td>32 (74.4)</td>
<td>16 (94.1)</td>
<td></td>
</tr>
<tr>
<td>Disseminated</td>
<td>12 (20.0)</td>
<td>11 (25.6)</td>
<td>1 (5.9)</td>
<td></td>
</tr>
<tr>
<td>Serum lactate dehydrogenase level</td>
<td></td>
<td></td>
<td></td>
<td>.6</td>
</tr>
<tr>
<td>Normal</td>
<td>54 (90.0)</td>
<td>38 (88.4)</td>
<td>16 (94.1)</td>
<td></td>
</tr>
<tr>
<td>High</td>
<td>6 (10.0)</td>
<td>5 (11.6)</td>
<td>1 (5.9)</td>
<td></td>
</tr>
<tr>
<td>Immunohistochemistryc</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bcl-2 positive, No. of patients/total No. of patients</td>
<td>51/60 (85.0)</td>
<td>39/43 (90.7)</td>
<td>12/17 (70.6)</td>
<td>.1</td>
</tr>
<tr>
<td>MUM-1 positive, No. of patients/total No. of patients</td>
<td>23/41 (56.1)</td>
<td>18/29 (62.1)</td>
<td>5/12 (41.7)</td>
<td>.3</td>
</tr>
<tr>
<td>Complete response</td>
<td></td>
<td></td>
<td></td>
<td>.2</td>
</tr>
<tr>
<td>Yes</td>
<td>41 (68.3)</td>
<td>27 (62.8)</td>
<td>14 (82.4)</td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>19 (31.7)</td>
<td>16 (37.2)</td>
<td>3 (17.6)</td>
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<tr>
<td>Relapsed</td>
<td></td>
<td></td>
<td></td>
<td>.13</td>
</tr>
<tr>
<td>No</td>
<td>15 (36.6)</td>
<td>8 (29.6)</td>
<td>7 (50.0)</td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>26 (63.4)</td>
<td>19 (70.4)</td>
<td>7 (50.0)</td>
<td></td>
</tr>
<tr>
<td>Extracutaneous progression</td>
<td></td>
<td></td>
<td></td>
<td>.3</td>
</tr>
<tr>
<td>No</td>
<td>34 (56.7)</td>
<td>23 (53.5)</td>
<td>11 (64.7)</td>
<td></td>
</tr>
<tr>
<td>Yes, nodal only</td>
<td>9 (15.0)</td>
<td>6 (14.0)</td>
<td>3 (17.6)</td>
<td></td>
</tr>
<tr>
<td>Yes, visceral with or without nodal</td>
<td>17 (28.3)</td>
<td>14 (32.6)</td>
<td>3 (17.6)</td>
<td></td>
</tr>
<tr>
<td>Status</td>
<td></td>
<td></td>
<td></td>
<td>.001</td>
</tr>
<tr>
<td>Alive, disease free</td>
<td>16 (26.7)</td>
<td>5 (11.6)</td>
<td>11 (64.7)</td>
<td></td>
</tr>
<tr>
<td>Alive with disease</td>
<td>4 (6.7)</td>
<td>4 (9.3)</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Died of lymphoma</td>
<td>31 (51.7)</td>
<td>27 (62.8)</td>
<td>4 (23.5)</td>
<td></td>
</tr>
<tr>
<td>Died, other cause</td>
<td>9 (15.0)</td>
<td>7 (16.3)</td>
<td>2 (11.8)</td>
<td></td>
</tr>
<tr>
<td>Disease-specific survival rate, %</td>
<td></td>
<td></td>
<td></td>
<td>.002</td>
</tr>
<tr>
<td>3 y</td>
<td>53</td>
<td>43</td>
<td>77</td>
<td></td>
</tr>
<tr>
<td>5 y</td>
<td>41</td>
<td>26</td>
<td>77</td>
<td></td>
</tr>
</tbody>
</table>

a Data are given as number (percentage) unless otherwise indicated.

b Leg vs nonleg primary cutaneous diffuse large B-cell lymphoma, leg type. For 5-year survival rates, P values were calculated from a comparison of survival curves.

c Not available in all patients.

d Considered only in 41 patients who achieved a complete response.
Among 41 patients (68.3%) who achieved at any time a complete response, 26 (63.4%) experienced 1 or several relapses. Of 60 patients, 26 (43.3%) developed extracutaneous disease. The mean time until extracutaneous dissemination was 20 months. The dissemination was restricted to the lymph nodes in 9 patients. The remaining 17 patients had visceral progression associated with lymph node involvement (6 patients) or without (11 patients). The central nervous system was the most frequent site of visceral dissemination (7 patients). Other sites included the bones (2 patients), kidney (2 patients), liver (1 patient), spleen (1 patient), testis (1 patient), pancreas (1 patient), breast (1 patient), pelvis (1 patient), and brachial plexus (1 patient).

Thirty-one patients (51.7%) died of lymphoma, and 9 patients (15.0%) died of unrelated disease. Of 31 disease-specific deaths, 24 (77.4%) followed extracutaneous progression of the disease. Eight other deaths were considered disease-related despite the absence of obvious extracutaneous involvement. These included patients who developed fatal sepsis after chemotherapy and those who died of secondary infection, major cutaneous tumor bulk and ulceration, or major worsening of their general condition. The 3-year and 5-year disease-specific survival rates were 53% and 41%, respectively.

**PROGNOSTIC FACTORS**

In univariate analysis, disease-related death was statistically significantly associated with location on the leg \( (P = .003) \), disseminated distribution \( (P = .04) \), and the presence of multiple skin lesions at diagnosis \( (P = .004) \).

**CHARACTERISTICS OF PATIENTS AND OUTCOMES IN DIFFERENT PROGNOSTIC GROUPS**

Because the topographic subtype (leg vs nonleg) was the strongest prognostic factor, the main features at diagnosis and the follow-up data were subsequently analyzed according to the location of skin lesions (Table 1). Patients with the leg subtype were older and had more numerous skin lesions at diagnosis than patients with nonleg PCLBCL LT; they showed a tendency for less frequent response to therapy and more frequent relapses and visceral progressions. The 3-year disease-specific survival rates were 43% in the leg subtype group and 77% in the nonleg subtype group \( (P = .002) \). Kaplan-Meier lymphoma-specific survival curves according to the location of skin lesions are shown in the Figure.

The number of skin lesions at diagnosis also was a major distinctive factor for predicting survival in the entire

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**Table 2. Summary of Therapies**

<table>
<thead>
<tr>
<th>Therapy</th>
<th>First-line Therapies</th>
<th>Subsequent Therapies</th>
</tr>
</thead>
<tbody>
<tr>
<td>Radiation therapy</td>
<td>23 (38.3)b</td>
<td>3</td>
</tr>
<tr>
<td>Single-agent chemotherapy</td>
<td>1 (1.7)</td>
<td>2</td>
</tr>
<tr>
<td>Polychemotherapies without anthracycline</td>
<td>8 (13.3)c</td>
<td>5</td>
</tr>
<tr>
<td>Anthracycline-containing chemotherapy without rituximab</td>
<td>11 (18.3)d</td>
<td>7</td>
</tr>
<tr>
<td>Various combinations of anthracycline-containing chemotherapies and rituximab</td>
<td>11 (18.3)</td>
<td>1</td>
</tr>
<tr>
<td>Other</td>
<td>6 (10.0)e</td>
<td></td>
</tr>
</tbody>
</table>

*a Data are given as number (percentage).

b Associated with single-agent chemotherapy in 1 patient.
c Associated with radiation therapy in 1 patient.
d Associated with radiation therapy in 3 patients.
e Consisted of surgery in 3 patients, oral corticosteroid use in 1 patient, and no therapy in 2 patients.

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**Table 3. Results From the Multivariate Analysis**

<table>
<thead>
<tr>
<th>Result</th>
<th>Relative Risk (95% Confidence Interval)</th>
<th>( P ) Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Location of skin lesions</td>
<td>.02</td>
<td></td>
</tr>
<tr>
<td>Nonleg</td>
<td>1 [Reference]</td>
<td></td>
</tr>
<tr>
<td>Leg</td>
<td>3.3 (1.1-10.0)</td>
<td></td>
</tr>
<tr>
<td>No. of lesions</td>
<td>.05</td>
<td></td>
</tr>
<tr>
<td>Single</td>
<td>1 [Reference]</td>
<td></td>
</tr>
<tr>
<td>Multiple</td>
<td>2.3 (1.0-5.4)</td>
<td></td>
</tr>
</tbody>
</table>
Within this heterogeneous group of primary cutaneous lymphomas and a large proportion of large-cell lymphomas, we identified location on the leg as the main negative prognostic factor. Patients with leg tumors had a survival rate that differed by period of inclusion because rituximab was never used before 2002 and was used only rarely before 2004. Therefore, no long-term (>3-year) survival comparison was available at the end point. The 2-year survival rate differed between the 2 groups (group receiving various combinations of anthracycline-containing chemotherapies and rituximab, 81%; group receiving other therapies, 59%) without reaching a statistically significant difference (P=.3). However, the short-term outcome was more favorable in patients treated with various combinations of anthracycline-containing chemotherapies and rituximab. Among these 12 patients, all but 1 (91.6%) achieved a complete response (compared with 62% in the group receiving other therapies) (P=.05), and 10 of 11 patients had no relapse. At the end point, 9 of these patients were alive with a mean follow-up of 19 months (8 patients without disease and 1 patient with disease). 2 patients had died of lymphoma (1 patient of septicemia after chemotherapy and 1 patient of brain involvement), and 1 patient had died of unrelated disease. A similar comparative analysis between patients treated with anthracycline-containing chemotherapies without rituximab and other patients failed to disclose any difference in outcomes.

ROLE OF THERAPY

Although no variable related to therapy was statistically significantly associated with survival in this retrospective study, we further analyzed patients who received at any time various combinations of anthracycline-containing chemotherapies and rituximab (12 patients) and compared them with those who received other therapies only (48 patients). These 2 groups did not differ by age, location, or number of skin lesions. They strongly differed by period of inclusion because rituximab was never used before 2002 and was used only rarely before 2004. Therefore, no long-term (>3-year) survival comparison was available at the end point. The 2-year survival rate differed between the 2 groups (group receiving various combinations of anthracycline-containing chemotherapies and rituximab, 81%; group receiving other therapies, 59%) without reaching a statistically significant difference (P=.3). However, the short-term outcome was more favorable in patients treated with various combinations of anthracycline-containing chemotherapies and rituximab. Among these 12 patients, all but 1 (91.6%) achieved a complete response (compared with 62% in the group receiving other therapies) (P=.05), and 10 of 11 patients had no relapse. At the end point, 9 of these patients were alive with a mean follow-up of 19 months (8 patients without disease and 1 patient with disease). 2 patients had died of lymphoma (1 patient of septicemia after chemotherapy and 1 patient of brain involvement), and 1 patient had died of unrelated disease. A similar comparative analysis between patients treated with anthracycline-containing chemotherapies without rituximab and other patients failed to disclose any difference in outcomes.

We report herein the largest study of PCLBCL LT, to our knowledge, and provide new data on its clinicopathologic features and prognostic factors. In addition, we provide preliminary results comparing outcomes in patients treated with classic vs new therapeutic regimens.

Most PCBCLs, including almost all small-cell lymphomas and a large proportion of large-cell lymphomas, have an indolent clinical course. However, a subset of PCBCLs with a predomiance of large cells comprises aggressive lymphomas. This finding led researchers to look for discriminating prognostic factors within this heterogeneous group of primary cutaneous lymphomas. Small case series first identified the location on the leg as a criterion of aggressiveness. In further multicenter studies, round-cell morphological features (ie, the predominance of large cells with round nuclei over large cells with cleaved nuclei) and Bcl-2 protein expression were identified as additional adverse prognostic factors.

In the WHO-EORTC classification, the term primary cutaneous diffuse large B-cell lymphoma, leg type was introduced besides primary cutaneous follicle center cell lymphoma and primary cutaneous marginal zone B-cell lymphoma to designate PCBCLs with a predomiance of large cells and a less favorable prognosis. Primary cutaneous diffuse large B-cell lymphoma, leg type was primarily defined on the basis of morphological features by the presence of confluent sheets of large cells with round nuclei (ie, centroblasts and immunoblasts). Primary cutaneous diffuse large B-cell lymphoma with a predominance of large cleaved cells and fewer centroblasts was classified within the group of primary cutaneous follicle center cell lymphoma. In addition, it was specified that PCLBCL LT arises on the leg in most (but not all) cases and demonstrates strong Bcl-2 expression. The role of Bcl-2 expression for classifying these lymphomas remained unclear.

Using these criteria, we found that PCLBCL LT is characterized by a poor prognosis, a high proportion of Bcl-2 expression (85%), an advanced age at onset (median age, 77 years), and a frequent location on the leg (72% in 43 cases, including 5 cases with lesions on the leg and at other sites). The 3-year and 5-year disease-specific survival rates in the entire group were 53% and 41%, respectively.

Survival rates in the present study (Table 1) were lower than those in previous reports. The Italian study Group for Cutaneous Lymphomas recently reported a 5-year survival rate of 73% in 51 patients with PCLBCL LT, including 6 patients without leg lesions. Kodama et al reported a 5-year survival rate of 61.7% in 40 Austrian patients with Bcl-2–negative PCLBCL LT, 32 of whom had disease on the leg. Such differences in survival may result from variations in management and therapy or from differences in baseline characteristics of patients resulting from various selection biases. Although patients included in the Austrian study did not differ in age from our patients, those included in the Italian series were younger (median age, 70 years). In addition, only patients who had 6 months of follow-up without extracutaneous dissemination were included in the Italian series. In our study, patients were included on the basis of negative initial staging, irrespective of further outcome. Some older patients had multiple and bulky tumors on the legs, could receive only palliative care, and died early after diagnosis. These patients were not excluded from the study and affected the survival rate in the entire series.

We identified location on the leg as the main negative prognostic factor. Patients with leg tumors had a
3-year disease-specific survival rate of 43%, compared with 77% in patients with nonleg PCLBCL LT. This result confirms and extends previous reports of the aggressiveness of primary cutaneous large B-cell lymphoma of the leg, as defined in the previous EORTC classification. However, the prognosis of nonleg PCLBCL LT (Figure) seems poorer than that of primary cutaneous follicle center lymphoma or primary cutaneous marginal zone B-cell lymphoma, which are characterized by 5-year survival rates of 95% to 100%. Therefore, it seems preferable to classify these lymphomas on a morphological basis within the group of PCLBCL LT, as proposed in the recent WHO-EORTC classification, rather than in the group of primary cutaneous follicle center cell lymphoma, as in the previous EORTC classification.

The second negative prognostic factor in our study was the presence of multiple skin lesions. Although the number of skin lesions had no prognostic value in the Austrian series, 2 previous studies on aggressive PCBLs identified multiple skin lesions as an important adverse prognostic factor. This is in accord with earlier studies of different types of cutaneous or noncutaneous lymphomas that underlined the prognostic value of variables related to tumor burden. In the present study, the 3-year disease-specific survival rate was 39% in patients with multiple skin lesions vs 77% in patients with only 1 lesion (P = .004). Most patients with leg involvement had multiple tumors. However, those with only 1 tumor on a leg had a favorable prognosis. Whether these patients may be first treated with less aggressive procedures such as radiation therapy alone remains questionable.

In the present study, PCLBCL LT showed intermediate or positive staining for MUM-1 protein in most cases and consistently expressed Bcl-2 protein. This finding confirms that the expression of MUM-1 and Bcl-2 characterizes not only primary cutaneous large B-cell lymphomas of the leg, as previously demonstrated, but also PCLBCL LT defined on a morphological basis. Bcl-2 expression was almost universal in cases located on the leg and was observed in most nonleg cases (Table 1). Overall, only 9 of 60 cases had negative Bcl-2 staining. Bcl-2-negative PCLBCL LT is rare and has been poorly characterized to date. Kodama et al described 9 cases using the term large B-cell lymphoma, other. Four cases were located outside of the leg. No difference in survival was observed between these 9 patients (5-year survival, 50%) and 40 patients with typical Bcl-2–positive PCLBCL LT (5-year survival, 61.7%). We found similar results, with 3-year survival rates of 43% in Bcl-2–negative patients vs 54% in Bcl-2–positive patients (P = .8). Although these results need to be confirmed in larger series, it seems suitable to include all of these cases within the group of PCLBCL LT as defined morphologically by confluent sheets of large round B-cells, irrespective of Bcl-2 staining.

Primary cutaneous diffuse large B-cell lymphoma, leg type is an aggressive lymphoma that requires effective therapies. This seems to be a difficult challenge in view of the advanced age of many patients. Historically, some of these patients received only palliative care, radiation therapy, or nonaggressive chemotherapies. However, the report of the effectiveness of various combinations of anthracycline-containing chemotherapies and rituximab in older patients with noncutaneous diffuse large B-cell lymphomas led to changes in the French practices regarding the cutaneous counterparts of these lymphomas. The rationale for this attitude was enhanced by the demonstration that rituximab was able to overcome Bcl-2–associated resistance to chemotherapy, which coincided with findings that most PCLBCL LT strongly expressed Bcl-2. In the present study, 12 patients who received various combinations of anthracycline-containing chemotherapies and rituximab were retrospectively compared with 48 patients who received other treatments. Although the follow-up was insufficient to objectively determine a statistically significant difference in survival, more favorable short-term outcomes were observed with various combinations of anthracycline-containing chemotherapies and rituximab, particularly in patients with multiple skin tumors.

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