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Primary cutaneous lymphomas: applicability of current classification schemes (European Organization for Research and Treatment of Cancer, World Health Organization) based on clinicopathologic features observed in a large group of patients

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Classification of primary cutaneous lymphomas (PCLs) is the subject of ongoing controversy. Based on a series of 556 patients, the applicability of the European Organization for Research and Treatment of Cancer (EORTC) classification for PCLs was assessed and compared to the proposed World Health Organization (WHO) classification of hematologic malignancies. The large majority of patients could be properly classified according to the scheme proposed by the EORTC. Comparison of estimated 5-year survival for specific diagnostic categories of PCLs demonstrated nearly complete concordance of the present results with those of the EORTC study for most of the indolent cutaneous T-cell lymphomas and cutaneous B-cell lymphomas, whereas differences were found for mycosis fungoides-associated follicular mucinosis and Sezary syndrome. A few patients with newly described entities (CD8$^+$ epidermotropic cytotoxic T-cell lymphoma, primary cutaneous natural killer/T-cell lymphoma) could not be classified according to the EORTC scheme. Comparison of the EORTC with the WHO classification showed that the EORTC scheme allows a more precise categorization of the patients, especially for cutaneous B-cell lymphoma. In conclusion, the study confirmed that the EORTC classification allows a better management of patients with PCL. Small amendments to that classification should be carried out to account for recently described entities and to unify some of the diagnostic categories. (Blood. 2002;99:800-805)

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Introduction

Primary cutaneous lymphomas (PCLs) represent distinct clinical and histopathologic subtypes of extranodal T- and B-cell lymphomas. Until recently, they have been classified only according to classification schemes devised mainly for nodal non-Hodgkin lymphomas such as the Kiel or the Revised European-American Lymphoma (REAL) classifications.[1,2] Recently, the European Organization for Research and Treatment of Cancer (EORTC)–Cutaneous Lymphoma Project Group proposed a new classification of PCLs based on a combination of clinical, histologic, and immunophenotypic criteria.[3] This classification has the aim of allowing a more uniform diagnosis and treatment of patients with PCLs. The EORTC classification has been the subject of criticism and debates,[4,5] and some dermatopathologists and hematopathologists have suggested that PCLs should be classified according to the scheme currently being developed by the World Health Organization (WHO).[6] Beside lymphoid neoplasms the proposed WHO classification includes myeloid, histiocytic, and mast cell neoplasms.[6]

Prognostic categories in the EORTC classification are based on data from 626 patients collected in the Dutch Registry for Cutaneous Lymphoma. A subsequent study by Grange and colleagues tested the clinical validity of the EORTC classification in 158 patients with PCLs other than mycosis fungoides, Sezary syndrome, and lymphomatoid papulosis.[7] With the exception of these 2 studies, prognostic analyses on patients with PCLs were performed only in small groups of patients.[8-10]

The aim of our study was to evaluate the applicability of the EORTC classification for patients with PCLs and to compare it to the proposed WHO classification. In addition, we compared survival data observed in our group of patients with those reported in the EORTC study.

Patients and methods

Data from 556 patients collected in the files of the Department of Dermatology of the University of Graz between 1960 and 1999 were included in this study. Excluded from the study were 109 patients without adequate follow-up data as well as 11 unclassifiable cases. Of the 556 patients, 353 (63.5%) were men and 203 (36.5%) were women. Age ranged from 3 to 91 years (mean age, 56.5; median, 59). Follow-up data varied from a minimum of 6 to a maximum of 605 months (mean, 50.8; median, 38). Primary skin involvement was defined as the presence of cutaneous lymphoma without nodal or visceral involvement after complete staging procedures. Staging procedures were performed with standard methods available at time of first diagnosis, including, when applicable, physical examination, blood cell count, chest radiograph, thoracic computed tomographic scan, abdominal ultrasound sonography, abdominal computed tomographic scan, sonography of superficial lymph nodes, positron electron tomography, and bone marrow biopsy. In each case, the original diagnosis was revised by at least 2 dermatopathologists (L.C., H.K.) based on clinicopathologic criteria. Patients with so-called "small plaque parapsoriasis" were not included in this study.

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Submitted April 11, 2001; accepted August 8, 2001.

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Clinical and follow-up data

Clinical data analyzed included age of the patients, sex, date of first diagnosis, duration of follow-up, and status of the disease at last follow-up examination. The following parameters were selected to assess the status of the patient at the end point of follow up: A−, alive and well; A+(s), alive with skin disease alone; A+(v), alive with systemic spread; D+, dead of disease; D−, dead, unrelated to disease.

All patients were treated with one or more treatment modalities including surgical excision of the lesions, local radiotherapy, UV-radiation therapy, psoralen-UV-A (PUVA) therapy, retinoid-PUVA therapy, extracorporal photopheresis, interferon α2a, combination of one or more of the aforementioned therapies, and mono- or polychemotherapy. Many patients received different therapies at different times. The effects of therapy were not included in our study.

Histology, immunohistology, molecular biology

Sections with a maximum thickness of 4 μm stained with hematoxylin and eosin, Giemsa, and periodic acid-Schiff were available for standard histologic evaluation.

Immunophenotyping was performed on formalin-fixed, paraffin-embedded tissue sections using a 3-step immunoperoxidase technique as described previously,[11] with a standard panel of primary antibodies.

In all cases where a paraffin block could be retrieved, the analysis of the T-cell receptor (TCR) and immunoglobulin heavy chain (IgH/J_H) genes rearrangement were performed using a standard polymerase chain reaction (PCR) technique[12,13] with minor modifications as published previously.[14] Only cases with clear-cut clinicopathologic and molecular features were included in the study. In particular, the presence of a monoclonal T- or B-cell population in patients presenting with lesions otherwise nondiagnostic on clinicopathologic grounds was not considered sufficient for a diagnosis of T- or B-cell lymphoma, respectively.

Statistical analysis

End point was the death of the patient, either disease-related or nonspecific. For surviving patients, the study end point was December 31, 1999 or the last available follow-up prior to this date.

Statistical analyses were performed using the SPSS/PC statistical software package (SPSS, Chicago, IL). Survival curves were calculated using the life table method of Kaplan and Meier. Univariate disease-free interval analysis was calculated using Kaplan-Meier tables and the log-rank test. $P \leq .05$ was considered to indicate statistical significance.[15]

Results

Of the total group 409 patients (74%) had a cutaneous T-cell lymphoma (CTCL), and 147 (26%) had a cutaneous B-cell lymphoma (CBCL). Classification of cutaneous lymphoma, sex, median age, median follow-up, and estimated 5-year survival are summarized in Table 1. Cases were primarily classified according to categories listed in the EORTC classification, when possible. Diagnoses and classification in our patients and comparison to corresponding categories in the EORTC and the proposed WHO classifications are summarized in Figure 1.

CTCLs

Mycosis fungoides. 281 patients (M:F = 2.02:1). Age range: 9-88 years (mean, 58.1; median, 61). Follow-up: range, 6-605 months (mean, 64; median, 38). Estimated 5-year survival: 89%. EORTC classification: mycosis fungoides. WHO classification: mycosis fungoides/Sezary syndrome.

Mycosis fungoides-associated follicular mucinosis. 25 patients (M:F = 4:1). Age range: 33-74 years (mean, 52.3; median, 51). Follow-up: range, 6-262 months (mean, 78.3; median, 51). Estimated 5-year survival: 93%. EORTC classification: mycosis fungoides-associated follicular mucinosis. WHO classification: mycosis fungoides/Sezary syndrome.

Pagetoid reticulosis. 1 male patient. Age: 68 years; he developed generalized skin disease 60 months after first diagnosis. EORTC classification: pagetoid reticulosis. WHO classification: mycosis fungoides/Sezary syndrome.

Lymphomatoid papulosis. 43 patients (M:F = 1.38:1). Age range: 4-86 years (mean, 44.4; median, 47). Follow-up: range, 6-366 months (mean, 67.7; median, 48). Estimated 5-year survival: 100%. EORTC classification: lymphomatoid papulosis. WHO classification: anaplastic large cell lymphoma, T/null cell, primary cutaneous type.

$CD30^+$ cutaneous large T-cell lymphoma. 18 patients (M:F = 3.5:1). Age range: 3-70 years (mean, 50.9; median, 57). Follow-up: range, 6-201 months (mean, 51.4; median, 30). Estimated 5-year survival: 100%. EORTC classification: $CD30^+$

Table 1. Diagnosis of cutaneous lymphoma, clinical features, and follow-up data in our group of patients

Diagnosis	No. of patients	Sex (M:F)	Median age, y (range)	Median follow-up, mo (range)	Estimated 5-y survival, %
T-cell lymphomas					
Mycosis fungoides	281	2.02:1	61 (9-88)	38 (6-605)	89
Mycosis fungoides-associated follicular mucinosis	25	4:1	51 (33-74)	51 (6-262)	93
Pagetoid reticulosis	1	1:0	68	60	100
Lymphomatoid papulosis	43	1.38:1	47 (4-86)	48 (6-366)	100
CD 30^+ cutaneous large T-cell lymphoma	18	3.5:1	57 (3-70)	30 (6-201)	100
Sezary syndrome	22	4.5:1	66.5 (32-91)	28 (7-115)	33
$CD30^-$ cutaneous large T-cell lymphoma	2	1:1	55 (34-76)	9 (7-11)	100
Pleomorphic small/medium-sized cutaneous T-cell lymphoma	7	0.75:1	65 (53-80)	41 (7-227)	80
Primary cutaneous NK cell lymphoma	3	2:1	63 (31-66)	31 (30-50)	0
Primary cutaneous $CD8^+$ epidermotropic cytotoxic T-cell lymphoma	4	3:1	61.5 (48-65)	30.5 (7-36)	0
Subcutaneous panniculitislike T-cell lymphoma	3	0.5:1	39 (29-48)	54 (44-75)	100
B-cell lymphomas					
Primary cutaneous follicle center cell lymphoma	60	0.76:1	58.5 (20-89)	41.5 (6-313)	94
Primary cutaneous immunocytoma/marginal zone B-cell lymphoma	62	1.69:1	55.5 (17-86)	48 (7-292)	98
Large B-cell lymphoma of the leg	23	0.76:1	72 (43-86)	13 (8-168)	58
Plasmacytoma	2	2:0	52.5 (50-55)	21 (12-30)	100

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Present study	EORTC classification	WHO classification
Mycosis fungoides	Mycosis fungoides	Mycosis fungoides/Sézary syndrome
	Mycosis fungoides-associated follicular mucinosis	
	Pagetoid reticulosis	
Sézary syndrome	Sézary syndrome	
Lymphomatoid papulosis	Lymphomatoid papulosis	Anaplastic large cell lymphoma, primary cutaneous type
Large cell CTCL, $CD30^+$	Large cell CTCL, $CD30^+$	
CTCL, pleomorphic, small/medium-sized	CTCL, pleomorphic, small/medium-sized	Peripheral T-cell lymphoma, not otherwise characterized
Primary cutaneous $CD8^+$ epidermotropic cytotoxic T-cell lymphoma	Large cell CTCL, $CD30^-$	
Large cell CTCL, $CD30^-$		
Primary cutaneous NK/T-cell lymphoma		NK/T-cell lymphomas
Subcutaneous panniculitis-like T-cell lymphoma	Subcutaneous panniculitis-like T-cell lymphoma	Subcutaneous panniculitis-like T-cell lymphoma
Primary cutaneous immunocytoma/marginal zone B-cell lymphoma	Primary cutaneous immunocytoma/marginal zone B-cell lymphoma	Extranodal marginal zone lymphoma of MALT type
Primary cutaneous follicle center cell lymphoma	Primary cutaneous follicle center cell lymphoma	Follicular lymphoma
		Diffuse large B-cell lymphoma
Primary cutaneous large B-cell lymphoma of the leg	Primary cutaneous large B-cell lymphoma of the leg	
Primary cutaneous plasmacytoma	Primary cutaneous plasmacytoma	Extramedullary plasmacytoma

Figure 1. Diagnoses and classification of primary cutaneous lymphomas observed in our patients and comparison to corresponding categories of the EORTC and the proposed WHO classifications. Overlapping boxes identify entities that would be included in more than one category in those two classification schemes.

cutaneous large T-cell lymphoma. WHO classification: anaplastic large cell lymphoma, T/null cell, primary cutaneous type.

Sezary syndrome. 22 patients (M:F = 4.5:1). Age range: 32-91 years (mean, 65.1; median, 66.5). Follow-up: range, 7-115 months (mean, 39.6; median, 28). Estimated 5-year survival: 33%. EORTC classification: Sezary syndrome. WHO classification: mycosis fungoides/Sezary syndrome.

$CD30^-$ cutaneous large T-cell lymphoma. One male and one female patient. Age range: 34-76 years (mean, 55; median, 55). Follow-up: range, 7-11 months (mean, 9; median, 9). Both patients had skin disease alone after the follow-up of 7 and 11 months, respectively. EORTC classification: $CD30^-$ cutaneous large T-cell lymphoma. WHO classification: peripheral T-cell lymphoma, not otherwise characterized.

Subcutaneous "panniculitislike" T-cell lymphoma. 3 patients (M:F = 0.5:1). Age range: 29-48 years (mean, 38.7; median, 39). Follow-up: range: 44-75 months (mean, 57.7; median, 54). Estimated 5-year survival: 100%. EORTC classification: subcutaneous "panniculitislike" T-cell lymphoma (provisional entity). WHO classification: subcutaneous "panniculitislike" T-cell lymphoma.

Pleomorphic small/medium-sized cutaneous T-cell lymphoma. 7 patients (M:F = 0.75:1). Age range: 53-80 years (mean, 65.4; median, 65). Follow-up: range, 7-227 months (mean, 83.1; median, 41). Estimated 5-year survival: 80%. EORTC classification: pleomorphic small/medium-sized cutaneous T-cell lymphoma (provisional entity). WHO classification: peripheral T-cell lymphoma, not otherwise characterized.

Primary cutaneous natural killer cell lymphoma. 3 patients (M:F = 2:1). Age range: 31-66 years (mean, 53.3; median, 63). Follow-up: range, 30-50 months (mean, 37; median, 31). Estimated 5-year survival: 0%. EORTC classification: $CD30^-$ cutaneous large T-cell lymphoma. WHO classification: cutaneous natural killer cell

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lymphoma (NK/T-cell lymphoma); peripheral T-cell lymphoma, not otherwise characterized.

Primary cutaneous CD8⁺ epidermotropic cytotoxic T-cell lymphoma. 4 patients (M:F = 3:1). Age range: 48-65 years (mean, 59; median, 61.5). Follow-up: range, 7-36 months (mean, 26; median, 30.5). Estimated 5-year survival: 0%. EORTC classification: CD30⁻ cutaneous large T-cell lymphoma; pleomorphic small/medium-sized cutaneous T-cell lymphoma. WHO classification: peripheral T-cell lymphoma, not otherwise characterized.

CBCLs

Primary cutaneous follicle center cell lymphoma. 60 patients (M:F = 0.76:1). Age range: 20-89 years (mean, 58.1; median, 58.5). Follow-up: range, 6-313 months (mean, 67.8; median, 41.5). Estimated 5-year survival: 94%. Forty-five patients presented lesions with a diffuse pattern of growth, and 15 with a follicular pattern. EORTC classification: primary cutaneous follicle center cell lymphoma (PCFCCL). WHO classification: follicular lymphoma; diffuse large B-cell lymphoma.

Primary cutaneous immunocytoma/marginal zone B-cell lymphoma. 62 patients (M:F = 1.69:1). Age range: 17-86 years (mean, 51.3; median, 55.5). Follow-up: range, 7-292 months (mean, 67.7; median, 48). Estimated 5-year survival: 98%. EORTC classification: primary cutaneous immunocytoma (marginal zone B-cell lymphoma). WHO classification: extranodal marginal zone B-cell lymphoma (mucosa-associated lymphoid tissue [MALT]-type lymphoma).

Large B-cell lymphoma of the leg. 23 patients (M:F = 0.76:1). Age range: 43-86 years (mean, 70.6; median, 72). Follow-up: range, 8-168 months (mean, 32; median, 13). Estimated 5-year survival: 58%. EORTC classification: primary cutaneous large B-cell lymphoma of the leg. WHO classification: diffuse large B-cell lymphoma.

Plasmacytoma. 2 men aged 50 and 55 years (mean and median, 52.5). Follow-up: range, 12-30 months (mean and median, 21). One patient had skin disease after a follow-up of 12 months; the second had systemic spread after a follow-up of 30 months. EORTC classification: primary cutaneous plasmacytoma (provisional entity). WHO classification: extramedullary plasmacytoma.

Discussion

The classification of PCLs is the subject of ongoing debates.[4,16-18] At present, 2 main classification schemes are used. The first one was proposed by the EORTC in 1997,[3] and the second is based on the classification of hematologic malignancies proposed by WHO, which is an update of the REAL classification.[6] Overall analysis of our data shows that patients with PCL are better classified according to the EORTC classification than to the scheme proposed by WHO. Figure 1 summarizes the entities that could be observed in our group of patients and corresponding EORTC and WHO categories. The need for a special classification of lymphomas arising primary in the skin is supported also by the notion of the existence of special adhesion receptors ("homing receptors") regulating the traffic of normal and neoplastic lymphocytes, thus underlying the concept of "organ-bound" lymphomas.[19]

Although in the EORTC classification of PCL was defined as presence of disease limited to the skin for at least 6 months after complete staging procedures, based on 2 main reasons we defined it as negative staging at presentation. First, aggressive lymphomas that arise within the skin may show dissemination before a period of 6 months; second and most important, patients need to be treated at presentation, thus a clear-cut diagnosis must be established immediately, not 6 months afterward.

Comparison of data for specific diagnostic categories demonstrated nearly complete concordance of our results with those of the EORTC study for most of the indolent CTCLs.[3] A major difference, however, was found concerning mycosis fungoides-associated follicular mucinosis. In fact, we could observe no statistically significant difference in survival among patients with "classic" mycosis fungoides and those with mycosis fungoides-associated follicular mucinosis (log-rank; $P = .22$), whereas in the EORTC study the estimated 5-year survival of mycosis fungoides-associated follicular mucinosis was 70%, as compared to 87% for patients with "classic" mycosis fungoides.[3] Thus, our data do not support distinction of this variant of mycosis fungoides into a separate category. It is also interesting that in our study, one patient with localized pagetoid reticulosis developed generalized skin lesions 5 years after the onset of the disease. Localized pagetoid reticulosis with subsequent onset of generalized lesions has been described in the past,[20] and might show a prognosis similar to that of mycosis fungoides,[21] underlying the need for long-term follow-up for these patients.

A difference in survival data between our study and that of the EORTC was found for patients with Sezary syndrome. Our estimated 5-year-survival rate of 33% is similar to those reported by Bernengo et al[22] and by Marti et al.[23] In contrast, the estimated 5-year survival reported by the EORTC group was only 11%.[3] This discrepancy is probably due to the use of different diagnostic criteria, resulting in selection of different groups of patients.[24,25] It should be underlined, however, that the prognosis of patients with Sezary syndrome is much worse than that of patients with mycosis fungoides, and that treatment modalities are different, supporting the inclusion of these patients into separate categories, as in the EORTC classification, and in contrast to the WHO classification.

Interestingly, an estimated 5-year survival of 100% could be found for our patients with subcutaneous "panniculitislike" T-cell lymphoma, in contrast to the data reported in the EORTC classification.[3] It should be underlined, however, that we observed only 3 patients with this entity and that in our cases, reclassification of older biopsies, reported originally as "lupus panniculitis" or "nonspecific lobular panniculitis," resulted in considerably longer survival rates. In fact, molecular analyses performed retrospectively demonstrated the presence of the same monoclonal population of T lymphocytes in biopsies previously considered to be nondiagnostic. It seems likely that subcutaneous "panniculitislike" T-cell lymphoma is underdiagnosed, and that many patients indeed experience a chronic course of disease with prolonged survival.[26,27]

A small percentage of CTCLs (16 cases) in our study could be classified into 4 diagnostic categories present only in part in the EORTC and WHO schemes (pleomorphic small/medium-sized CTCL, CD30⁻ cutaneous large T-cell lymphoma, primary cutaneous CD8⁺ epidermotropic cytotoxic T-cell lymphoma, and primary cutaneous NK/T-cell lymphoma). CD30⁻ cutaneous large T-cell lymphoma and pleomorphic small/medium-sized T-cell lymphoma are mentioned in the EORTC classification as aggressive and provisional entities, respectively. These cases would have been included in the category of peripheral T-cell lymphoma, not otherwise characterized if classified according to the proposed WHO classification.[6] The clear differences in clinicopathologic presentation, prognosis, and treatment between these 2 groups, however, support their inclusion into separate categories. The

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so-called $CD8^+$ epidermotropic cytotoxic T-cell lymphoma[28] and the primary cutaneous NK/T-cell lymphoma[29] are not listed within the EORTC and WHO classifications. These cases are included in the categories of pleomorphic small/medium-sized CTCL and $CD30^-$ cutaneous large T-cell lymphoma in the EORTC classification[3] and in the category of peripheral T-cell lymphoma, not otherwise characterized and extranodal NK/T-cell lymphoma, nasal type in the WHO classification, respectively.[6] Although sufficient data to completely characterize these entities are still lacking, patients present with different clinicopathologic and immunophenotypic features, thus suggesting that classification into distinct categories might be appropriate.

There was almost complete concordance between our data and those reported in the EORTC study concerning prognostic features for all 3 major categories of CBCL considered in the EORTC classification. PCFCCLs are reported as the most common type of primary CBCL in the EORTC classification,[3] whereas in our group of patients primary cutaneous immunocytoma/marginal zone B-cell lymphoma was slightly more represented. These data most likely reflect regional variation in the incidence of different lymphoma subtypes. Concerning PCFCCL, one main problem is that many cases classified in this group in the EORTC classification would be included among the diffuse large B-cell lymphomas in the WHO classification.[6] In fact, the majority of cutaneous cases are characterized by a diffuse pattern of growth with predominance of medium to large centrocytes and centroblasts, and a follicular pattern is seen only in a minority of cases.[30,31] However, patients with PCFCCL show an indolent course, irrespective of the histopathologic and cytomorphologic features of the infiltrate, and aggressive therapy is not justified. Primary cutaneous immunocytoma/marginal zone B-cell lymphoma would be classified among the extranodal marginal zone lymphoma of the MALT type in the WHO classification.[6] However, this group includes B-cell lymphomas arising in such disparate organs as the stomach, thyroid, and salivary glands among others. Many of these lymphomas arise in the setting of chronic antigenic stimulation due to microbacterial antigens (ie, *Helicobacter pylori*) or autoimmune diseases.[32,33] Although the role of *Borrelia burgdorferi* has been suggested for a small proportion of CBCLs,[34] in most cases neither bacterial nor autoimmune diseases can be observed. Moreover, treatment modalities are different from those applied for the extracutaneous MALT-type lymphomas, thus suggesting that they should be considered as a separate entity. However, the term "immunocytoma" for cutaneous cases may be the source of confusion, because in the proposed WHO classification it is used for a distinct group of systemic lymphomas often associated with Waldenstrom macroglobulinemia.[6] Another controversy concerns the distinction of primary cutaneous marginal zone lymphoma from immunocytoma. Although we believe that there are clinical and histopathologic differences between the 2 groups,[14] similarities in prognosis and treatment suggested the EORTC to classify these patients in one single category.[3]

In the proposed WHO classification cases of extramedullary plasmacytoma are mentioned only as variants of plasmacytomas, without reference to the site of onset,[6] whereas in the EORTC classification plasmacytoma is included only as a provisional entity. Based on data from the literature and from our 2 patients, the prognosis of primary cutaneous plasmacytoma seems to be good,[35-37] justifying its inclusion into the group of indolent CBCLs as a distinct clinicopathologic entity.

In our study, we could find similar survival data for patients with primary cutaneous large B-cell lymphoma of the leg, when compared to those published in the EORTC study.[3] There has been much debate concerning the terminology of this type of cutaneous lymphoma, especially because a distinct, albeit small proportion of the cases arises at body sites other than the legs.[38-41] However, primary cutaneous large B-cell lymphoma of the leg represents a category that should be clearly separated from the "diffuse" type of PCFCCL, because cytomorphology and prognosis are clearly different. Moreover, most cases do indeed arise on the legs. The term "large B-cell lymphoma of the leg" underlines one distinctive clinical feature of this cutaneous lymphoma, and can be paralleled to terminology of other lymphomas currently classified according to the site of onset (ie, nasal lymphoma, hepatosplenic lymphoma, etc).

In conclusion, our study confirmed that most primary CTCLs and CBCLs can be classified according to the entities listed in the EORTC classification. It may be necessary to perform small amendments to this classification to take into account recently described entities and to unify some of the diagnostic categories.

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2002 99: 800-805
doi:10.1182/blood.V99.3.800

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Blood (print ISSN 0006-4971, online ISSN 1528-0020), is published weekly by the American Society of Hematology, 2021 L St, NW, Suite 900, Washington DC 20036.
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