Primary cutaneous lymphomas
Rein Willemze, MD

Primary cutaneous lymphomas have a distinct clinical behavior and prognosis, and therefore require a different therapeutic approach, as compared with their primary nodal equivalents. The European Organization for Research and Treatment of Cancer (EORTC) classification for primary cutaneous lymphomas recognizes a limited number of cutaneous T-cell lymphomas and cutaneous B-cell lymphomas and is at present the best guide to optimal management and treatment of these conditions. Herein, the relationship between the EORTC classification and the recently published World Health Organization classification is discussed, and recent developments regarding the main types of cutaneous T-cell lymphomas and cutaneous B-cell lymphomas recognized in the EORTC classification are presented. Curr Opin Oncol 2000, 12:419–425 © 2000 Lippincott Williams & Wilkins, Inc.

Department of Dermatology, Leiden University Medical Center, Leiden, The Netherlands
Correspondence to Rein Willemze, MD, Dept. of Dermatology, B1-Q-93, Leiden University Medical Center, PO Box 9600, 2300 RC Leiden, The Netherlands; e-mail: willemze.dermatology@lumc.nl

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Abbreviations
ALCL anaplastic large cell lymphomas
CBCL cutaneous B-cell lymphomas
CTCL cutaneous T-cell lymphomas
EORTC European Organization for Research and Treatment of Cancer
LTCL large T-cell lymphomas
LyP lymphomatoid papulosis
MF mycosis fungoides
REAL Revised European-American Classification for Lymphoid Neoplasms
TGF-β transforming growth factor-beta
WHO World Health Organization

Cutaneous lymphomas represent clonal proliferations of neoplastic T or B lymphocytes, which can involve the skin primarily or secondarily. The term primary cutaneous lymphoma refers to cutaneous T-cell lymphomas (CTCL) and cutaneous B-cell lymphomas (CBCL), which present in the skin with no evidence of extracutaneous disease at the time of diagnosis [1]. They represent, after the group of gastrointestinal lymphomas, the second most common group of extranodal lymphomas, with an estimated annual incidence of 0.5 to 1 per 100,000. Primary cutaneous lymphomas often have a completely different clinical behavior and prognosis compared with their nodal counterparts with or without secondary cutaneous involvement, and therefore require a different approach to treatment. In addition, differences in the presence of specific translocations and in the expression of onco-genes, viral sequences or antigens (e.g., Epstein-Barr virus antigen), and adhesion receptors involved in tissue-related lymphocyte homing (e.g., cutaneous lymphocyte antigen) have been reported [1]. Such differences underscore the fact that these primary cutaneous lymphomas represent a distinct group of lymphomas and may explain, at least in part, their different clinical behavior. In addition, they may be used as additional diagnostic criteria to differentiate between primary and secondary cutaneous lymphomas. For instance, the t(2;5) translocation is found in a subset of systemic CD30-positive anaplastic large cell lymphomas (ALCL), but not or rarely in primary cutaneous ALCL [2,3]. Therefore, demonstration of a t(2;5) or expression of the corresponding gene product anaplastic lymphoma kinase in a cutaneous CD30-positive ALCL is strongly suggestive of secondary cutaneous involvement. Perhaps the most unique feature of these primary cutaneous lymphomas is that they can be seen and can be biopsied easily, allowing an optimal correlation between clinical appearance and clinical behavior on the one hand and histologic, phenotypical, and genetic aspects on the other. In the last decade, such an approach resulted in the delineation of distinct types of CTCL and CBCL, which formed the basis of new classifications for the group of primary cutaneous lymphomas [1,4].

Classification of primary cutaneous lymphomas
Until recently, classification systems for non-Hodgkin lymphomas, such as the Kiel classification [5] and the Working Formulation [6], were based on histologic criteria, and within the different categories distinction by site was not made. Since these classification systems did
not recognize the special character of primary cutaneous lymphomas, these lesions were not uncommonly diagnosed incorrectly and treated inappropriately with unnecessarily aggressive treatment regimens. In recent years, awareness has grown that malignant lymphomas should be viewed as a group of disease entities, defined by a constellation of morphologic, immunologic, genetic, and clinical criteria, that extranodal lymphomas are not identical to their nodal counterparts, and that the site of presentation is important. These basic concepts are found both in the European Organization for Research and Treatment of Cancer (EORTC) classification for primary cutaneous lymphomas [1], the Revised European-American Classification for Lymphoid Neoplasms (REAL) [7] and the recently published World Health Organization (WHO) classification [8].

The EORTC classification is the only classification that is designed specifically for the group of primary cutaneous lymphomas. It contains a limited number of well-defined types of CTCL and CBCL, which together account for more than 95% of all primary cutaneous lymphomas (Table 1). In addition, it contains a number of provisional entities that mostly display characteristic histologic features, but for which a distinctive clinical presentation and clinical outcome have not yet been defined. Distinction is made between primary cutaneous lymphomas with an indolent, intermediate, or aggressive clinical behavior. The clinical validity of this new classification has now been substantiated by two large studies, including follow-up data of more than 800 patients with a primary cutaneous lymphoma [1,9••]. With the introduction of the REAL and the WHO classifications, the need for a separate classification for the group of primary cutaneous lymphomas has been disputed [10,11]. Moreover, there is consensus between the EORTC and the WHO classifications regarding the classification of most CTCL (see Table 1). However, in addition to well-defined entities, the WHO classification still contains some broad histologic categories, such as the group of diffuse large B-cell lymphomas and the group of peripheral T-cell lymphomas, unspecified, which are in fact broad histologic subgroups, and in which distinction by site is not made (see Table 1).

Because it delineates more completely defined and recognizable disease entities, the EORTC classification is at present the best guide to optimal treatment and management of these primary cutaneous lymphomas, and the best vehicle to evaluate the efficacy of existing and novel therapies, and to investigate risk factors in the development and progression of these lymphomas [12].

<table>
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*Includes anaplastic, immunoblastic, and large pleomorphic CD30-positive CTCL. †Includes immunoblastic and large pleomorphic CD30-negative CTCL. ‡For cases with a predominance of small neoplastic B-cells. §For rare cases showing a follicular growth pattern. ¶For cases showing a predominance of large neoplastic B-cells (most cases). WHO: lymphomas included in the main list of lymphoid neoplasms are shown in **boldface** type; variants and subtypes to be discussed in the WHO book are shown in *italic*. ALCL, anaplastic large cell lymphoma; CTCL, cutaneous T-cell lymphoma; NK, natural killer.
Herein, recent development regarding the main types of CTCL and CBCL recognized in the EORTC classification will be presented.

**Cutaneous T-cell lymphoma**

**Mycosis fungoides**

Mycosis fungoides (MF), the most common type of CTCL, is an indolent type of CTCL that slowly evolves through patch, plaque, and tumor stages, before lymph nodes and visceral organs become involved, and ultimately rapidly progressive and fatal disease develops [13]. Previous studies already indicated that patients with limited patch/plaque stage MF have a similar long-term life expectancy as an age-, sex-, and race-matched control population [14]. Recent studies confirmed that disease progression occurs in only a minority of patients. In a study of 309 unselected MF patients, the risk of disease progression at 10 years gradually increased from 10% in patients presenting with limited patch/plaque stage MF to 70% in patients presenting with skin and lymph node involvement, and amounted 38% for the total study group [15]. In that study, stage at diagnosis, complete remission after initial treatment and the presence of follicular mucinosis appeared independently predictive of both disease-specific survival and disease progression. In a recent study, demonstration of circulating clonal T cells also proved to be an independent prognostic parameter [16].

Mycosis fungoides patients with only skin lesions are treated traditionally with skin-directed therapies, including topical steroids, psoralen plus ultraviolet A, ultraviolet B, topical nitrogen mustard, and total skin electron beam irradiation, whereas multi-agent chemotherapy is generally used only in patients with extracutaneous involvement [13]. Early aggressive systemic chemotherapy is associated with considerable morbidity but does not result in improved survival [17]. At present, the efficacy of several new immunomodulatory treatment regimens, including fusion toxins (DAB389IL-2), novel synthetic retinoids (Targretin®), and cytokines (interleukin-12) is being evaluated [18•,19,20,21••]. It remains to be determined which categories of MF patients are most likely to benefit from these new therapies.

**Sézary syndrome**

Sézary syndrome is defined historically by the triad of erythroderma, generalized lymphadenopathy, and the presence of neoplastic T cells (Sézary cells) in skin, lymph nodes, and peripheral blood. There is still no consensus on the diagnostic criteria of Sézary syndrome. Demonstration of at least 1000 circulating Sézary cells per square millimeter is often used as a decisive criterion but is not entirely specific for Sézary syndrome [22,23]. In the EORTC classification, increased numbers of CD3+, CD4+ T cells with a CD4/CD8 ratio greater than 10 and evidence of a T-cell clone in the peripheral blood are suggested as useful additional criteria [1]. Recent studies confirmed the importance of demonstrating circulating clonal T cells in the diagnosis of Sézary syndrome [24]. Methotrexate, a combination of chlorambucil and prednisone, and extracorporeal photopheresis, either alone or in combination with other treatment modalities, have been reported to be effective. In recent studies, extracorporeal photopheresis has been suggested as the therapy of first choice [23]. However, overall response rates in patients treated with extracorporeal photopheresis vary between 53% and 83%, which may be attributed to differences in treatment as well as patient selection [25]. Prospective randomized trials are required to define which patients will benefit most from this type of treatment.

**Primary cutaneous CD30-positive large T-cell lymphoma and lymphomatoid papulosis**

Primary cutaneous CD30-positive lymphoproliferations represent the second most common group of CTCL (see Table 1). This group includes two closely related conditions considered to form a spectrum of disease: the group of CD30-positive primary cutaneous large T-cell lymphomas (LTCL), including anaplastic and nonanaplastic cases, and lymphomatoid papulosis (LyP) [26]. Primary cutaneous CD30-positive LTCL generally present with one solitary or few clustered skin lesions. They have the tendency to disappear spontaneously and to relapse in the skin, rarely disseminate to extracutaneous sites, and have an excellent prognosis (disease-specific 5-year-survival: 96%) [26,27••]. Recently, new guidelines have been developed for the treatment of these primary cutaneous CD30-positive LTCL [27••]. Based on studies of 219 primary and secondary cutaneous CD30-positive lymphoproliferations, including 79 patients with a primary cutaneous CD30-positive LTCL and 118 patients with LyP, it was found that not only patients with LyP, but also all patients with a primary cutaneous CD30-positive LTCL who had been treated with systemic chemotherapy demonstrated one or several skin relapses afterwards. It was concluded that patients with skin-restricted CD30-positive LTCL, even in the setting of multifocal disease, should not be treated routinely with multi-agent chemotherapy. If spontaneous regression does not occur, these patients can best be treated with radiotherapy if there are only a few lesions, or with low-dose methotrexate in cases of LyP (Fig. 1).

Lymphomatoid papulosis is a chronic, recurrent, self-healing papulonodular eruption with the histologic features of a CD30-positive CTCL, but almost without exception a benign clinical course. Recent studies suggested a role for transforming growth factor-beta (TGF-β) in the spontaneous resolution of skin lesions in
LyP. A tumor cell line derived from an ALCL developing from LyP demonstrated a mutation in the TGF-β type I receptor, which rendered these cells insensitive to the growth inhibitory effects of TGF-β [28•].

Because of its typically benign clinical behavior, inclusion of LyP as a separate entity in the EORTC classification has been much disputed. However, since differentiation between cutaneous CD30-positive ALCL and LyP is often not possible by histologic criteria alone, and additional clinical criteria are needed to make a definite diagnosis and to determine the type of treatment, hemato-oncologists should be aware of the different entities within this spectrum of primary cutaneous CD30-positive lymphoproliferations.

Primary cutaneous CD30-negative large T-cell lymphoma
Primary cutaneous CD30-negative LTCL without prior or concurrent MF represent a distinct group of CTCL with an aggressive clinical behavior [1,29]. Histologically, these lymphomas show nodular or diffuse infiltrates with a predominance of medium-sized to large pleomorphic T cells. Clinically, most patients present with or rapidly develop generalized plaques or tumors. Multi-agent chemotherapy is the first choice of treatment. Only in patients presenting with solitary or localized skin lesions should radiotherapy be considered. These primary cutaneous CD30-negative LTCL must be differentiated from CD30-negative CTCL with a predominance of small or medium-sized pleomorphic T cells, which have a much better prognosis [1,9••,29], and are included as a provisional entity in the EORTC classification. In the WHO classification, both groups are lumped together in the group of peripheral T-cell lymphoma, unspecified, which raises concerns about potential overtreatment of these primary cutaneous CD30-negative small or medium-sized pleomorphic T-cell lymphomas.

Cutaneous lymphomas with a CD8-positive or CD56-positive phenotype
Most CTCL have a CD3+, CD4+, CD8– phenotype. Cutaneous lymphomas with a CD3+, CD4–, CD8+ or with a CD56+ phenotype are rare and have not been included separately in the EORTC classification. CTCL with the characteristic clinical features of MF or a primary cutaneous CD30-positive LTCL expressing a CD3+, CD4–, CD8+ T-cell phenotype have the same clinical behavior as cases with a CD3+, CD4+, CD8– phenotype. Recent studies demonstrated that primary
cutaneous CD8-positive epidermotropic pleomorphic T-cell lymphomas with a cytotoxic phenotype represent a distinct clinicopathologic entity with an aggressive clinical behavior [30•,31]. CD56-positive hematologic malignancies not uncommonly present in the skin. This group is still ill-defined and includes cases of nasal and nasal-type natural killer (NK) and T-cell lymphomas (EBV+, TIA-1+, granzyme B+) [32], cases of blastic NK-cell lymphoma or leukemia [33], and a recently described group of CD3–, CD56+, CD4+ lymphomas (EBV–, TIA-1–, granzyme B–) [34–36]. Although skin lesions may sometimes be the only manifestation at the time of diagnosis, patients with these CD56-positive malignancies characteristically have a very poor clinical outcome, despite aggressive treatment.

Cutaneous B-cell lymphomas

In the EORTC classification, three main groups of CBCL are distinguished: primary cutaneous immunocytoma or marginal zone B-cell lymphoma, the group of primary cutaneous follicle center cell lymphoma, and primary cutaneous large B-cell lymphoma of the leg.

The term primary cutaneous immunocytoma was based on the terminology of the Kieli classification; these lymphomas are now generally designated as primary cutaneous marginal zone B-cell lymphoma. Although skin relapses are uncommon, dissemination to extracutaneous sites or lymphoma-related deaths have not been reported. Radiotherapy or excision is the first choice of treatment. Association with Borrelia burgdorferi infection has been reported [37], and antibiotic therapy—allegedly also in rare patients presenting with multifocal skin infections in gastric mucosa-associated lymphoid tissue (MALT) lymphoma—may result in clinical improvement [38,39].

The term primary cutaneous follicle center cell lymphoma was introduced in 1987 as an encompassing term for cutaneous lymphomas that were composed of centroblasts and (large) centrocytes and were classified as either centroblastic/centrocytic or centroblastic according to the updated Kieli classification [40]. Clinically, most patients present with localized skin lesions on the head or trunk. Histologically, most cases show a proliferation of large cleaved B cells and would be classified as diffuse large B-cell lymphoma in the REAL and the WHO classification (see Table 1). Notwithstanding, these primary cutaneous follicle center cell lymphomas rarely disseminate to extracutaneous sites (approximately 5%) and have an excellent prognosis [40–43]. Radiotherapy is the first choice of treatment not only in patients presenting with localized skin lesions, but probably also in rare patients presenting with multifocal skin lesions [44•].

A primary cutaneous large B-cell lymphoma of the leg clearly differs from the diffuse large B-cell lymphomas arising on the head and the trunk, as described earlier, and have therefore been included as a separate category in the EORTC classification [1,45]. Primary cutaneous large B-cell lymphoma of the leg particularly affect elderly people and show a higher relapse rate and a more unfavorable prognosis [9••,45], particularly in patients presenting with multiple skin lesions either at one or both legs [44•]. Histologically, most cases show a predominance of centroblasts and immunoblasts (large noncleaved, round cells) rather than large centrocytes (large cleaved and multilobulated cells), and consistently express bcl-2 protein [44•,46]. In the WHO classification, these lymphomas are included in the group of diffuse large B-cell lymphomas.

Conclusions

In the last decade, many well-defined types of CTCL and CBCL have been delineated, which have been included in the EORTC classification for primary cutaneous lymphomas. Recognition of these entities has contributed to better diagnosis and treatment. It is fortunate to note that also other recently proposed classification schemes (REAL and WHO classification) recognize that malignant lymphomas should be considered as a group of disease entities and that the site of presentation is important. Whereas there is consensus between the EORTC and WHO classification about the categorization of almost 90% of patients with a CTCL, there is still considerable confusion and disagreement regarding the terminology and classification of the group of CBCL [10–12]. However, since there is common awareness that most patients with a CBCL have an excellent prognosis, this current controversy is to a great extent a semantic discussion. It is expected that unravelling of the molecular mechanisms underlying the development and progression of these CBCL will result in a better insight into the origin of the different types of CBCL, and consequently a consensus will develop regarding the terminology and classification of these conditions.

References and recommended reading

Papers of particular interest, published within the annual period of review, have been highlighted as: • Of special interest •• Of outstanding interest


10 To test the clinical validity of the EORTC classification for primary cutaneous lymphomas and to identify prognostic factors of survival, 158 primary cutaneous lymphomas other than mycosis fungoides and Sézary’s syndrome are evaluated. Multivariate analysis indicated that the EORTC classification and the extent of skin lesions are independent prognostic factors for these primary cutaneous lymphomas.


20 Review of existing and many novel topical as well as systemic therapies in patients with mycosis fungoides and Sézary’s syndrome.


24 The authors describe the results of a phase I dose escalation trial with recombinant human interleukin-12 in patients with mycosis fungoides and Sézary’s syndrome. Subcutaneous administration of recombinant human interleukin-2 twice weekly was well tolerated and induced significant clinical responses in five of nine patients (overall response rate 56%). Regression of skin lesions was associated with increased numbers of CD8+ cytotoxic T cells.


30 Review of 219 primary and secondary cutaneous CD30-positive lymphoproliferative disorders, including 79 patients with a primary cutaneous CD30-positive (anaplastic) large T-cell lymphomas and 118 patients with lymphomatoid papulosis. The results of this study confirm that both conditions have an excellent prognosis and are intimately related. New guidelines for management and treatment are provided.

31 Schieman WP, Pfeifer WM, Levi E, et al.: A deletion in the gene for trans-


33 Studies on a tumor cell line derived from a CD30-positive anaplastic large cell lymphoma, which had developed in a patient with lymphomatoid papulosis. The authors demonstrated a mutation in the TGF-β1 type I receptor, which rendered these cells insensitive to the growth inhibitory effects of TGF-β. The results of these studies suggest a role for TGF-β in the spontaneous resolution of skin lesions in lymphomatoid papulosis.


The authors report that most patients with a primary CBCL presenting with multifocal skin lesions have an excellent prognosis. The usage of systemic chemotherapy in these patients is critically evaluated, and new guidelines for management and treatment are presented.
