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Bekkenk, M.W.

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Bekkenk, Marcel Willem

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Alterum illud ignorari non oportet, quod non omnibus aegris eadem auxilia conveniunt
(Een ander belangrijk punt is dat niet alle aandoeningen met hetzelfde medicijn moeten worden behandeld)
Celsus — De Medicina, Liber III

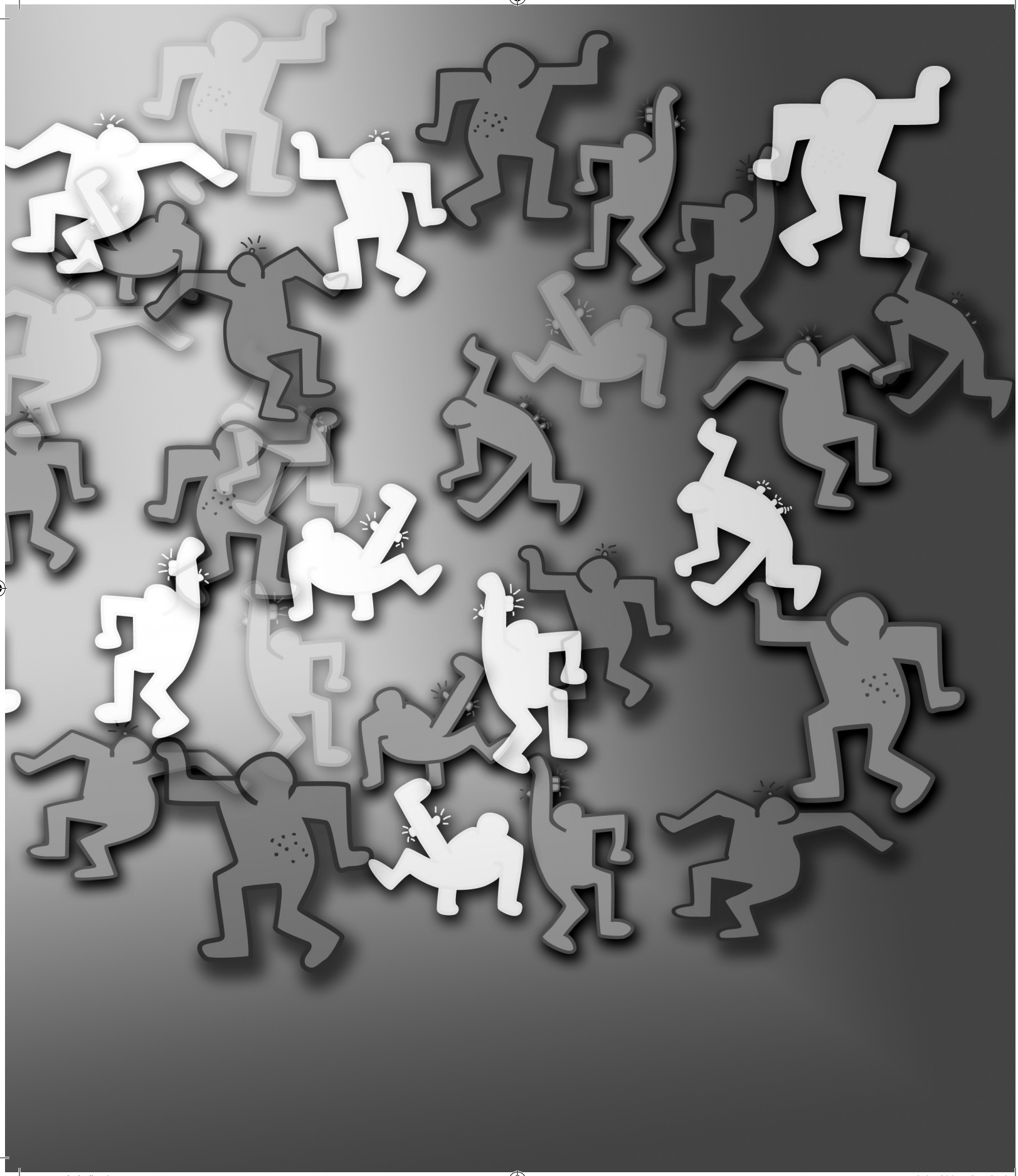
Voor mijn ouders, Pauline, Marijn en Hugo

Contents

List of Abbreviations

ALCL	Anaplastic large cell lymphoma
ALK	Anaplastic lymphoma kinase
AML	Acute myeloid leukemia
BNK	Blastic natural killer-cell lymphoma
CBCL	Cutaneous B-cell lymphoma
CD	Cluster Designation
CI	Confidence interval
C(H)OP	Combination chemotherapy (Cyclophosphamide, (Adriamycin), Oncovin and Prednisone)
CLA	Cutaneous leukocyte antigen
CNS	Central Nervous System
CTCL	Cutaneous T-cell lymphoma
EBER	EBV encoded non-coding RN`A
EBV	Epstein-Barr Virus
EMA	Epithelial Membrane Antigen
EORTC	European Organisation for Research and Treatment of Cancer
GSL	Granulomatous slack skin lymphoma
LPD	Lymphoproliferative Disorder
LyP	Lymphomatoid Papulosis
LTCL	Large T-cell lymphoma
MAC	Multiagent chemotherapy
MF	Mycosis Fungoides
MPO	Myeloperoxidase
NK	Natural killer
PCMZL	Primary cutaneous marginal zone B-cell lymphoma
PCFCCL	Primary cutaneous Follicle center cell lymphoma
PCLBCL-leg	Primary cutaneous Large B-cell lymphoma of the leg
PCI	Primary cutaneous Immunocytoma
pDC-type 2	precursor plasmacytoid dendritic cell type 2
PUVA	Psoralen-UVA
PTL, NOS	Peripheral T-cell lymphoma, not otherwise specified
REAL	Revised European-American Classification of Lymphoid Neoplasms
RR	Relative risk
RT	Radiotherapy
SS	Sezary Syndrome
SPTL	Subcutaneous Panniculitis-like T-cell lymphoma

t	Translocation
TCL-1	T-cell Lymphoid proto-oncogene 1
TCR	T-cell receptor rearrangement
TIA-1	T-cell intracytoplasmic antigen-1
UV	Ultraviolet
WHO	World Health Organisation



chapter 1

Introduction

Primary cutaneous lymphomas are a group of lymphoproliferative disorders, mostly derived from T-cells or B-cells, which present in the skin with no evidence of extracutaneous disease at the time of diagnosis Primary cutaneous lymphomas have a different clinical presentation, clinical behaviour and prognosis as compared to the histologically similar systemic lymphomas involving the skin secondarily, and require a different type of treatment. For that reason classification systems for non-Hodgkin lymphomas, such as the EORTC classification and the WHO classification, have included primary cutaneous lymphomas as separate entities. Comparison between both classification systems shows a great deal of consensus regarding the classification of cutaneous T-cell lymphomas (CTCL), although clinically significant differences remain. Differences in the classification and terminology of primary cutaneous B-cell lymphoma (CBCL) has resulted in confusion and ongoing debate.

The controversies between the EORTC and WHO classification schemes regarding the terminology and classification of the different types of CTCL and CBCL are addressed by the different studies included in this thesis. The studies presented in this thesis have been focused particularly on those groups of cutaneous lymphomas that are classified differently in the EORTC and WHO classification. The initial goal of our studies was to formulate suggestions for an updated version of the EORTC classification. However, very recently discussions between representatives of the EORTC and the WHO group resulted in a new classification for cutaneous lymphomas: the WHO-EORTC classification.

In this introductory chapter a historical overview of the classification of primary cutaneous lymphomas will be presented first. Differences between the EORTC and the WHO classification and the goals of the different studies addressing these controversies will be outlined. The results of these studies are presented in **CHAPTERS 2-8**. Based on the results of these studies and recent literature the new consensus WHO-EORTC classification and therapeutic guidelines for different types of primary cutaneous lymphoma will be presented (**CHAPTER 9**).

CLASSIFICATION OF CUTANEOUS LYMPHOMAS: A HISTORICAL OVERVIEW

In the early 1970s the only types of cutaneous lymphoma that had been rather well defined were mycosis fungoides (MF), including the classical Alibert-Bazin type and clinical variants as MF d'emblée and erythrodermic MF, and some related conditions as Sézary's syndrome (SS), pagetoid reticulosis and lymphomatoid papulosis (LyP). Reports on other types of cutaneous lymphoma were rare. These cutaneous lymphomas other than MF/SS were firmly believed to represent manifestations of systemic lymphoma and treated consistently.[1]

In 1975, based on the observation that the neoplastic cells in MF, SS and related conditions did not only have the same morphology showing atypical cells with cerebriform nuclei, but also a common T-cell phenotype, Edelson suggested the term CTCL for this group of diseases[2]. Within a short time this term gained wide acceptance, particularly in the USA. The

introduction of the CTCL concept can be considered as a landmark in the history of this group of diseases. However, a major disadvantage has been that in many subsequent studies no difference was made anymore between MF, SS and other T-cell neoplasms, which may vary considerably in clinical presentation and clinical behavior.

At about the same time when the CTCL concept was introduced, several European groups started to classify cutaneous lymphomas according to the criteria of the Kiel classification, a classification system used by hematopathologist for the classification of nodal lymphomas.[3] It was then found that many types of CBCL and CTCL other than classical MF and SS can present in the skin without any evidence of extracutaneous disease at the time of diagnosis. It appeared that these primary cutaneous lymphomas often have a completely different clinical behavior and prognosis compared to morphologically similar lymphomas arising in lymph nodes, and therefore require a different type of treatment.[4,5,6] In addition, differences in the presence of specific translocations and in the expression of oncogenes, viral sequences or antigens (eg Epstein-Barr Virus (EBV)), and adhesion receptors involved in tissue-related lymphocyte homing were found.[7,8,9] Such differences underscored that these primary cutaneous lymphoma represent a distinct group, and may explain, at least in part, their different clinical behavior. Perhaps most important, it appeared that different types of CTCL and CBCL with a different clinical behavior and different therapeutic requirements may have an identical histologic appearance. This implies that histological features should always be combined with clinical and immunophenotypical data, before a definite diagnosis (classification) can be made.
In the last decade such an approach resulted in the delineation of several new types of CTCL and CBCL, and formed the basis of the European Organization for Research and Treatment of Cancer (EORTC) classification for primary cutaneous lymphomas.[10]

EORTC CLASSIFICATION

The EORTC classification is the only classification designed specifically for the group of primary cutaneous lymphomas (**TABLE 1**). It contains a limited number of well-defined types of CTCL and CBCL, which together comprise more than 95% of all primary cutaneous lymphomas, and some provisional entities, which have not yet been fully defined clinically[10]. Distinction is made between cutaneous lymphomas with an indolent, intermediate or aggressive clinical behavior. By including well-defined and recognizable disease entities, this classification provides the clinician with detailed information on staging, preferred mode of treatment, clinical behavior and prognosis, and may serve as a useful guide to optimal management and treatment. The clinical significance of this classification has been validated by several large studies containing over 1300 patients with a primary cutaneous lymphoma.[10,11, 12, 13]

TABLE 1. Classification of disease entities of the EORTC in the WHO classification

EORTC-CLASSIFICATION	WHO CLASSIFICATION
CTCL	
Mycosis Fungoides	Mycosis Fungoides
Mycosis Fungoides variants • MF-associated follicular mucinosis • Pagetoid reticulosis • Granulomatous slack skin (provisional)	Mycosis Fungoides variants • MF-associated follicular mucinosis • Pagetoid reticulosis • Granulomatous slack skin
Sézary syndrome	Sézary syndrome
Lymphomatoid papulosis CTCL, large cell CD30+	Primary cutaneous CD30-positive T-cell lymphoprolif-erative disorders (primary cutaneous anaplastic large cell lymphoma, lymphomatoid papulosis; borderline lesions)
CTCL, large cell CD30- CTCL, pleomorphic small/medium cell (provisional)	Peripheral T-cell lymphoma, unspecified (most) Extranodal NK/T-cell lymphoma, nasal-type (some)
Subcutaneous panniculitis like T-cell lymphoma (provisional)	Subcutaneous panniculitis like T-cell lymphoma
CBCL	
Primary cutaneous immunocytoma/marginal zone B-cell lymphoma	Extranodal marginal zone B-cell lymphoma or MALT type lymphoma
Primary cutaneous follicle center cell lymphoma	Extranodal marginal zone B-cell lymphoma * Cutaneous follicle center lymphoma † Diffuse large B-cell lymphoma ‡
Primary cutaneous large B-cell lymphoma of the leg	Diffuse large B-cell lymphoma
Primary cutaneous plasmacytoma	Plasmacytoma
Intravascular large B-cell lymphoma	Diffuse large B-cell lymphoma (intravascular)

* For cases with a predominance of small neoplastic cells
† For cases showing a follicular growth pattern
‡ For cases showing a predominance of large neoplastic B-cells (most cases)

WHO classification

Whereas previous classifications for non-Hodgkin lymphomas used by hematopathologists, such as the Working Formulation[14] and the updated Kiel classification,[15] were based on purely histologic criteria, more recent classifications, such as the Revised European-American Classification for Lymphoid neoplasms (REAL classification)[16] and its successor the World Health Organization (WHO) classification,[17] also acknowledge that malignant lymphomas should be viewed as a group of disease entities, defined by a constellation of morphological, immunological, genetic and clinical criteria. In addition, it is recognized that the site of presentation is important, and that extranodal lymphomas are not identical to their nodal counterparts. The different types of primary cutaneous lymphoma included in the EORTC classification and their corresponding categories in the WHO classification are presented in **Table 1**. It illustrates that the WHO classification has adopted many types of CTCL from the EORTC classification. In fact, about 90% of all CTCL patients will be classified in an almost identical manner when either the EORTC or WHO classification is used. However, some important differences remain, which in some instances may have important therapeutic consequences. In contrast to the group of CTCL, the WHO classification did not adopt the categorization of CBCL from the EORTC classification. The discrepant views on the classification of CBCL have resulted in considerable debate and confusion.

In the remainder of this chapter the main characteristics of the different types of CTCL and CBCL included in the EORTC classification will be presented, differences between the EORTC classification and WHO classification will be highlighted and the questions addressed in the studies presented in **chapters 2-8** will be formulated.

Cutaneous T-cell lymphoma

Mycosis fungoides

Mycosis fungoides (MF) is characterized by the subsequent evolution of patches, plaques and tumors, and histologically by the presence of epidermotropic infiltrates of small to medium-sized atypical T-cells with cerebriform nuclei. It is the most common form of primary cutaneous lymphoma, accounting for approximately 45% of all primary cutaneous lymphomas.[10] The disease has a long natural history with usually an indolent course with slow progression over the years. Classically MF presents with patches and plaques on the trunk or extremities with a preferential localization in the "swim-suit" area. With progression of the disease (ulcerating) skin tumors may develop, and in a proportion of patients lymph nodes and visceral organs may get involved.

Both in the EORTC and WHO classification three variants of MF are included:

- Follicular or folliculotropic MF, a variant of MF, in which the atypical cells are folliculotropic rather than epidermotropic, and which characteristically presents in the

head and neck region. Because of the presence of deep (peri)follicular infiltrates rather than superficial epidermotropic infiltrates this type of CTCL is less accessible to skin-directed therapies. In most cases follicular mucinosis is observed. Recent studies showed that there is no difference in clinical presentation and clinical behaviour between cases with and cases without associated follicular mucinosis.[18,19] Therefore the term folliculotropic or follicular MF rather than MF-associated follicular mucinosis is preferred.[18]

- Pagetoid reticulosis is a rare variant of MF, characterized by the presence of localized patches or plaques, which are usually localized on the extremities, and are slowly progressive. In contrast to classical MF, extracutaneous dissemination or disease-related deaths have never been reported. Histologically, there is an intraepidermal proliferation of neoplastic T-cells, which may express either a CD3+, CD4+, CD8- or a CD3+, CD4-, CD8+ phenotype. CD30 is often expressed.[20,21]
- Granulomatous slack skin (GSS) is an extraordinarily rare type of CTCL characterized by the slow development of folds of lax skin and a granulomatous infiltrate with clonal T-cells.[22] Although it may develop in patients with otherwise classical MF, the exact relationship between GSS and MF is uncertain.

Sézary Syndrome

Sézary's syndrome (SS) 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.[23] There is at present no consensus on the diagnostic criteria of SS. Demonstration of at least 1000 Sézary cells per mm^3 is often used as a decisive criterion, but is not generally agreed upon.[24] Demonstration of clonal T-cells, the presence of an expanded CD4+ T-cell population resulting in a significantly increased CD4/CD8 ratio (>10) and cytogenetic evidence of a T-cell clone in the peripheral blood have been suggested as additional criteria.[10,25] Using these strict criteria the prognosis is generally poor with an overall 5-year-survival between 10% and 20%.[10] In a recent report of the International Society for Cutaneous Lymphomas (ISCL) slightly modified criteria for the diagnosis of SS have been suggested.[25]

Since there is consensus between the EORTC and WHO classification systems regarding the definition and classification of both MF (variants) and SS, these conditions are not further discussed in this thesis.

Spectrum of primary cutaneous CD30-positive lymphoproliferative disorders.

Primary cutaneous CD30-positive lymphoproliferative disorders represent the second most common group of CTCL, accounting for approximately 30% of all CTCL.[10] This group includes primary cutaneous CD30-positive large T-cell lymphoma, LyP, and borderline cases.

The term borderline case refers to cases with the clinical presentation of a CD30-positive large T-cell lymphoma, but with histologic features suggestive of LyP, and vice versa.[26] It follows that differentiation between primary cutaneous CD30-positive large T-cell lymphoma and lymphomatoid papulosis (LyP) cannot only be based on histologic criteria. The clinical appearance and course are used as decisive criteria for the definite diagnosis and choice of treatment. The overlapping clinical, histological, and immunophenotypical features have resulted in the view that CD30-positive cutaneous large T-cell lymphomas and LyP are parts of a spectrum of primary cutaneous CD30-positive lymphoproliferative disorders.[26,27]

Primary cutaneous CD30-positive (anaplastic) large T-cell lymphoma

Primary cutaneous CD30-positive (anaplastic) large cell lymphoma (ALCL) generally presents with solitary or localized nodules or tumors, and often shows ulceration. Multifocal lesions are seen in about 20% of the patients. Skin lesions may show partial or complete spontaneous regression, as in LyP. These lymphomas frequently relapse in the skin, but extracutaneous dissemination is uncommon.[28]

Radiotherapy is the first choice of treatment in patients presenting with a solitary or few localized nodules or tumors. Whether patients presenting with multifocal skin lesions should be treated with doxorubicin-based multiagent chemotherapy (MAC) or with a maintenance treatment of low-dose methotrexate as in LyP, is debatable. The prognosis is usually favorable with a 10-year disease-related survival exceeding 90%.[28,29]

Histologically, these lymphomas show diffuse nonepidermotropic infiltrates with cohesive sheets of large CD30-positive tumor cells. The CD30-positive neoplastic cells often express a CD4-positive T-cell phenotype with variable loss of CD2, CD5, and/or CD3. Unlike systemic CD30-positive lymphomas, most primary cutaneous CD30-positive large T-cell lymphomas express CLA (the weg), but do not express EMA and anaplastic lymphoma kinase (ALK), indicative of the 2;5 chromosomal translocation.[7,30,31]

In most cases the tumor cells have the characteristic morphology of anaplastic cells. Less commonly (20% to 25%), they have a pleomorphic or immunoblastic appearance. Based on prior studies suggesting that there are no differences in clinical presentation and clinical behavior between anaplastic and nonanaplastic cases, in the EORTC classification, the term primary cutaneous CD30-positive large T-cell lymphoma rather than primary cutaneous anaplastic large cell lymphoma is preferred[10]. Using the WHO classification, cases with a nonanaplastic morphology will often be classified as peripheral T-cell lymphoma, unspecified, in particular when CD30 staining has not been performed, and consequently be treated with unnecessarily aggressive modalities.[32,33,34] It is therefore of great clinical importance to ascertain that anaplastic and non-anaplastic cases have indeed the same clinical behaviour and prognosis.

Lymphomatoid papulosis

Lymphomatoid papulosis (LyP) is defined as a chronic, recurrent, self-healing papulonecrotic or papulonodular skin disease with histologic features suggestive of a (CD30-positive) malignant lymphoma[35]. Characteristically, the dermal infiltrates contain scattered or small clusters of large atypical, sometimes multinucleated or Reed-Sternberg-like, CD30-positive cells, interspersed in an extensive inflammatory infiltrate. The large atypical cells have the morphological and immunophenotypical characteristics of the neoplastic cells in the primary cutaneous CD30-positive large T-cell lymphomas.
Several studies demonstrated that in up to 20% of patients, LyP may be preceded by, associated with, or followed by another type of malignant (cutaneous) lymphoma, generally MF, a CD30-positive large T-cell lymphoma, or Hodgkin's lymphoma[36,37]. In a recent study however it was suggested that 80% of LyP patients will develop a systemic lymphoma within 15 years after diagnosis.[38] Risk factors for the development of a systemic lymphoma have however not yet been defined.

In chapter 2 treatment modalities and outcome, potential risk factors and long-term follow-up of 219 patients with primary and secondary CD30+ lymphoproliferative disorders were evaluated. Specific questions addressed in this study were:

- Are there differences in clinical outcome between primary cutaneous CD30-positive large T-cell lymphomas with an anaplastic or a non-anaplastic morphology?
- What is the risk to develop systemic lymphoma in patients within this spectrum of disease and which are potential risk factors?
- What is the best treatment of patients within this spectrum of disease, and in particular which patients should be treated with systemic multiagent chemotherapy? Based on the results of this study guidelines for diagnosis and treatment are provided.

Subcutaneous panniculitis-like T-cell lymphoma

Subcutaneous panniculitis-like T-cell lymphoma (SPTL) is a cytotoxic T-cell lymphoma, which preferentially infiltrates the subcutaneous tissue.[39,40] SPTL is a rare lymphoma, which can occur in adults as well as in young children. Patients generally present with solitary or multiple nodules and plaques, which mainly involve the legs, or less commonly the trunk. Systemic symptoms such as fever, fatigue and weight loss may be present. The disease may be complicated by a hemophagocytic syndrome, which is generally associated with a rapidly progressive course[41]. Histopathology reveals subcutaneous infiltrates simulating a panniculitis showing a mixture of neoplastic pleomorphic T-cells of various sizes and often many macrophages. Rimming of individual faT-cells by neoplastic T-cells is a helpful, though not completely specific diagnostic feature.[42] Necrosis, karyorrhexis and cytophagocytosis are common findings. Most cases show an α/β+, CD8+ T-cell phenotype with expression of

cytotoxic proteins, but up to 25% of cases have a γ/δ T-cell phenotype, are typically CD4-, CD8-, and often co-express CD56.[43] In contrast to SPTL with an α/β T-cell phenotype, SPTL with a γ/δ T-cell phenotype show neoplastic infiltrates that are not confined to the subcutaneous tissue, but may involve the epidermis and/or dermis as well, and invariably have a very poor prognosis. Based on these observations it has been suggested that SPTL with an γ/δ T-cell phenotype should be considered as a separate group.[43,44,45,46]

In CHAPTER 6 6 cases of CD56+ SPLT, five of which with a confirmed γ/δT-cell phenotype are evaluated. The pros and cons of classifying α/β+ and γ/δ+ SPTL separately will be discussed in CHAPTER 9.

Primary cutaneous CD30-negative T-cell lymphomas (non-MF/SS/SPTL)

Approximately 10% of CTCL cases do not belong to one of the entities described before.[10,47] These primary cutaneous CD30-negative CTCL (non-MF/SS/SPTL) form a heterogeneous group, both clinically and histologically. In general they have a poor prognosis.[10,11,12,48,49] In the EORTC classification these cases are classified as either primary cutaneous CD30-negative large cell CTCL or primary cutaneous CD30-negative small-medium sized pleomorphic CTCL. Distinction between these two categories, which is based on the presence of more or less than 30% large neoplastic T-cells is considered useful because of a significant difference in survival between both groups.[11,12,50,51] The EORTC classification does not include cases with prior or concurrent extracutaneous disease, and does not make further distinction between CD4+ and CD8+ cases. In the WHO classification the overwhelming majority of these CD30-negative large cell and small-medium sized pleomorphic CTCL are included in the group of peripheral T-cell lymphoma not otherwise specified (PTL, NOS), whereas rare cases are classified as extranodal NK/T-cell lymphoma, nasal-type (TABLE 1). The group of PTL, NOS includes both primary and secondary cutaneous cases, and further subdivision on the basis of cell size or phenotype is not made.

To find out if subdivision of these lymphomas on the basis of presentation with or without extracutaneous disease, cell size or phenotype is clinically significant, we evaluated the clinicopathologic features, treatment results and follow-up data of 82 patients with a PTL, NOS presenting in the skin. The results of this study are presented in CHAPTER 3.

CD56-positive hematologic neoplasms presenting in the skin

Cutaneous lymphomas are generally classified as cutaneous T-cell lymphoma (CTCL) or cutaneous B-cell lymphoma (CBCL). In European studies CTCL and CBCL account for approximately 75% and 25% of all (primary) cutaneous lymphomas, respectively[10,52]. The availability of monoclonal antibodies against CD56 that are active in paraffin sections has

resulted in the recognition of a subgroup of hematologic neoplasms mainly derived from natural killer (NK) cells or NK-like T-cells. These CD56+ hematologic neoplasms preferentially present at extranodal sites, not uncommonly the skin, and almost without exception have an extremely poor prognosis. In the WHO classification several groups of CD56+ neoplasms are distinguished, including extranodal NK/T-cell lymphoma, nasal-type and blastic NK-cell lymphoma.[17]

Extranodal NK/T-cell lymphomae, nasal-type is an EBV positive, nearly always extranodal lymphoma of small, medium or large cells usually with an NK-cell, or more rarely cytotoxic T-cell phenotype.[17] These lymphomas generally show prominent angiocentricity and angiodestruction often accompanied by extensive necrosis. These lymphomas have been reported most frequently in Asia and Central and South America, and are almost without exception strongly associated with EBV.[53] The term nasal-type is used to draw attention to the fact that the nasal cavity/nasopharynx is the prototypic site of involvement (previously designated as lethal midline granuloma), but identical neoplasms can be seen in other extranodal sites as well. The skin is the second most common site of involvement after the nasal cavity/nasopharynx.[54] Clinically, these lymphomas show plaques and tumors preferentially on the trunk and extremities, often with ulceration. These skin lesions are generally a secondary manifestation of the disease, but rare primary cutaneous cases have been reported as well.[55] In the EORTC such primary cutaneous lymphomas were not included as a separate entity, but included in the groups of primary cutaneous CD30-negative large T-cell lymphoma or in the group of small/medium-sized pleomorphic CTCL. The prognosis is poor, despite aggressive treatment and new therapeutic options should be investigated.[56,57]

Blastic NK-cell lymphoma is a clinically aggressive neoplasm, which most commonly presents in the skin with or without concurrent extracutaneous disease. Histologically, these neoplasms are characterized by a diffuse monotonous infiltrate of medium-sized cells resembling lymphoblasts or myeloblasts.[17] Characteristically, the neoplastic cells are positive for CD4 and CD56 and in some cases for TdT, but do not express surface CD3 and cytotoxic proteins, and are not associated with EBV.[17] Previous studies suggested these blastic NK-cell lymphomas are derived form precursor NK-cells.[17] More recent studies showed that the neoplastic cells strongly express the IL-3R alpha chain (CD123) and the lymphoid proto-oncogene TCL1 suggesting a derivation from early plasmacytoid dendritic cells rather than from NK-cell (precursors). CD4+, CD56+ hematodermic neoplasm[58] and early plasmacytoid dendritic cell leukemia/lymphoma[59] have been suggested as more appropriate terms for this condition.

Blastic NK-cell lymphoma is an aggressive disease with a poor prognosis. Although the skin may be the only site of involvement at presentation, early dissemination to the bone marrow and/or peripheral blood is the rule. Systemic chemotherapy usually results in a complete

remission, but quick relapses unresponsive to further chemotherapy are normally seen.

Recent studies suggest that patients can best be treated with regimens used in acute leukemias. Indeed, blastic NK-cell lymphoma should be differentiated above all from myeolomonocytic leukemia cutis, and is conceptually similar to so-called "aleukemic leukemia cutis".[42]

In addition to these two well-defined entities CD56 may be expressed in other types of lymphoma and leukemias such as primary cutaneous CD30+ LPD, SPTL, rare cases of PTL, NOS and myelomonocytic leukemias presenting primarily in the skin. CD56 expression in SPTL often indicates a γ/δ T-cell phenotype and an unfavorable prognosis. Whether CD56 expression in primary cutaneous CD30+ LPD also suggests a more unfavorable prognosis requires further study.

In an attempt to better define these different subgroups we evaluated the clinicopathologic and immunophenotypical data, treatment results and prognostic parameters of a large group of CD56+ haematologic neoplasms presenting in the skin, including 23 new cases and 130 cases from literature. The results are presented in **CHAPTER 4**. In **CHAPTER 5** a unique case of LyP showing co-expression of CD56 is described. Also in this chapter the question whether CD56 expression in primary cutaneous CD30+ lymphoproliferations is associated with a poor prognosis is addressed.

CUTANEOUS B-CELL LYMPHOMA

Unlike the situation for CTCL there is still considerable discrepancy between the EORTC and the WHO classification on primary cutaneous B-cell lymphoma.
In the EORTC classification three major subgroups are distinguished: primary cutaneous immunocytomas (PCI)/marginal-zone B-cell lymphomas (PCMZL), primary cutaneous follicle center cell lymphoma (PCFCCL) and primary cutaneous large B-cell lymphoma (PCLBCL) of the leg. In addition primary cutaneous intravascular B-cell lymphoma and primary cutaneous plasmacytoma are included as provisional entities.

Primary cutaneous immunocytoma / marginal zone B-cell lymphoma

PCI/PCMZL are indolent lymphomas composed of small B-cells including marginal zone (centrocyte-like) cells, lymphoplasmacytoid cells and plasma cells. Clinically most cases present with papules, plaques or nodules preferentially located on the trunk or extremities. Presentation with multifocal lesions is not uncommon.[60] Although cutaneous relapses occur frequently, extracutaneous dissemination is extremely rare. An association with *Borrelia Burgdorferia* is found in a minority of the European cases, but not in Asian cases or cases from the USA.[61,62,63,64] The prognosis is excellent with a five-year-survival close to 100%.[10]

In the EORTC classification the term PCI/PCMZL was used mainly to convey the message that PCMZL was a new name for cases designated previously as immunocytomas using the criteria of the Kiel classification. When the EORTC classification was composed the term PCI was preferred because the term MZL was still ill-defined and used in different ways. Some authors even suggested that not only PCI, but also most PCFCCL were derived from marginal zone B-cells and should be classified accordingly.[65] However, recent studies suggest that careful assessment of morphological and immunophenotypical features allows distinction between PCMZL and PCFCCL in most cases. Whereas PCFCCL consistently express bcl-6, rarely bcl-2 and CD10 to a variable degree, PCMZL almost consistently have a bcl-2+, bcl-6-, CD10- phenotype.[60,66] Using these additional markers it is most unlikely that PCFCCL are classified incorrectly as PCMZL. In addition, the term immunocytoma has become highly confusing, since in the WHO classification the extranodal immunocytomas as defined in the Kiel classification, have been renamed MZL, whereas in the term immunocytoma is used for a small group of systemic lymphoplasmacytic lymphomas generally associated with Waldenströms macroglobulinaemia. For these reasons the term PCMCL is now widely accepted as the most appropriate term for this type of cutaneous B-cell lymphoma.

Primary cutaneous follicle center cell lymphoma and primary cutaneous large B-cell lymphoma of the leg

In recent years the EORTC categories PCFCCL and PCLBCL-leg have been the subject of much debate. The term PCFCCL was introduced in 1987 as an encompassing term for cutaneous lymphomas, that were composed of cells with the morphology of follicle center cells, ie centroblasts and (large) centrocytes, and that were classified as either centroblastic/centrocytic or centroblastic according to the Kiel classification.[67] Whereas small and early lesions may show both small and large neoplastic B-cells and many admixed reactive T-cells, and may or may not have a (partly) follicular growth pattern, tumorous lesions generally show a predominance of large B-cells particularly large cleaved or multilobated B-cells, and less frequently a predominance of typical centroblasts and immunoblasts.[10,67,68] In contrast to nodal follicular lymphomas these PCFCCL do generally not express bcl-2 and are not associated with the t(14;18) translocation.[69,70] Clinically, most patients present with localized skin lesions on the head or trunk. In particular on the trunk these tumors may be surrounded by papules and slightly indurated plaques, which may precede the development of tumorous lesions for months or even many years. In the past PCFCCL with such a typical presentation on the back were referred to as "reticulohistiocytoma of the dorsum" or "Crosti's lymphoma".[71] Presentation with multifocal skin lesions is observed in approximately 14% of patients.[72] Dissemination to extracutaneous sites is uncommon. Irrespective of growth pattern (follicular or diffuse) or the number of blasts cells, these PCFCCL have an excellent prognosis with a 5-year-survival of over 95%.[10,11,12,62,68,71] Radiotherapy is the preferred mode of treatment

in particular in patients presenting with localised disease. Whether patients presenting with multifocal skin lesions should be treated with multiagent chemotherapy or rather with non-aggressive therapies is a matter of debate.[73,74]

The WHO-classification did not adopt this well-defined disease entity. In this classification PCFCCL with a (partly) follicular growth pattern were included as a variant of follicular lymphoma and designated cutaneous follicle center lymphoma, while cases with a diffuse growth pattern were classified as diffuse large B-cell lymphoma, which may result in overtreatment with multiagent chemotherapy rather than radiotherapy.

In the EORTC classification the term diffuse large B-cell lymphoma is only used for a special subgroup of patients presenting with tumours on the legs. These PCLBC-leg particularly affect elderly people, show a higher relapse rate and a more unfavourable prognosis as compared to PCFCCL with a diffuse large B-cell morphology (5-year-survival 95% vs 52%)[10,75]. For this reason they were included as a separate subgroup in the EORTC classification. Histologically, they show a predominance of centroblasts and immunoblasts rather than large cleaved cells, and consistently express the bcl-2 protein.[69] Although delineation of this subgroup based on site has been criticized, recent clinicopathologic and genetic studies further support that PCFCCL and PCLBCL-leg are distinct groups of CBCL. In contrast to PCFCCL with a diffuse large cell morphology, most PCLBCL-leg express Mum-1/IRF4[76] and the polycomb gene HPH[1,77] and frequently demonstrate translocations involving myc, bcl-6 and IgH genes.[78] Recent studies suggest that these PCLBCL-leg have an activated B-cell gene expression profile, while PCFCCL have a germinal center-like gene expression profile.[79]
The discrepant views of the EORTC and the WHO classification on the classification and terminology of PCFCCL and PCLBCL-leg is not merely a semantic discussion, but of great clinical importance. In fact, it concerns distinction between indolent (PCFCCL) and aggressive (PCLBCL-leg) types of CBCL, and consequently a choice between aggressive and non-aggressive types of treatment.

Therefore a large European study on primary cutaneous large B-cell lymphoma, including both PCLBCL-leg and PCFCCL with a predominance of large cells, was performed. The main goals were to identify independent risk factors, to find out whether PCLBCL-leg and PCFCCL have indeed a different clinical behaviour and to define additional prognostic parameters within these groups of CBCL. The results are described in **CHAPTER 6**.
Since there is uncertainty whether PCFCCL presenting with multifocal skin lesions have the same clinical behaviour and require the same therapeutic approach as PCFCCL presenting with localised disease, clinical and histological data of twenty-nine patients presenting with multifocal primary cutaneous B-cell lymphoma registered in the Dutch Cutaneous Lymphoma

Group were evaluated. The results of this study and proposals for management and treatment of this group is presented in CHAPTER 7.
Dissemination to extracutaneous sites is a rare event in CBCL. Because the development of CNS involvement in two subsequent patients with a CBCL, the frequency of dissemination and in particular CNS involvement was evaluated for the different groups of CBCL (CHAPTER 8).

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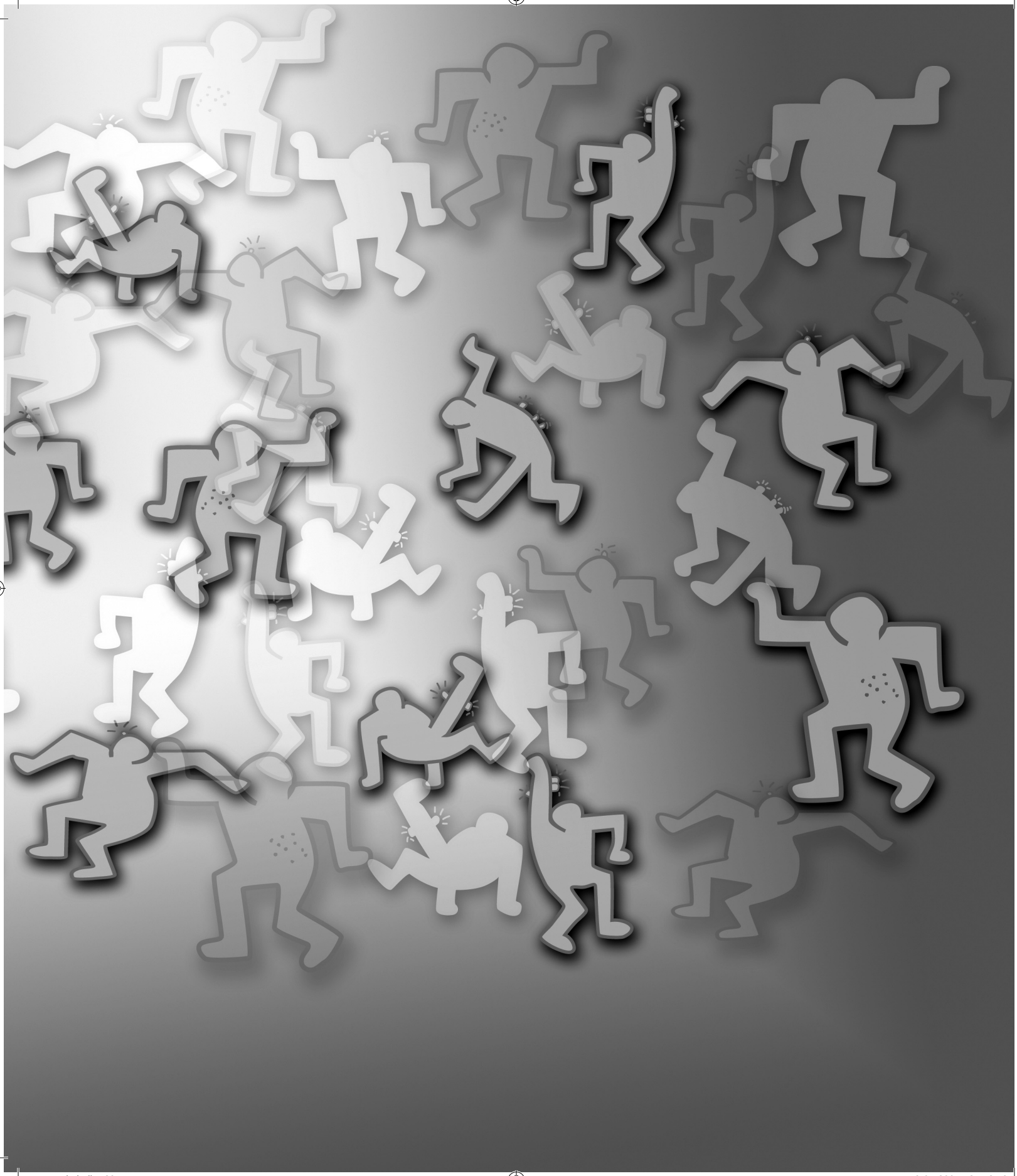

chapter 2

Primary and secondary cutaneous CD30+ lymphoproliferative disorders: a report from the Dutch Cutaneous Lymphoma Group on the long-term follow-up data of 219 patients and guidelines for diagnosis and treatment

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Marcel W. Bekkenk [1]
Françoise A. M. J. Geelen [2]
Pieter C. van Voorst Vader [3]
Freerk Heule [4]
Marie-Louise Geerts [5]
Willem A. van Vloten [6]
Chris J. L. M. Meijer [2]
Rein Willemze [1]

1. Department of Dermatology, Leiden University Medical Center, Leiden, the Netherlands
2. Departments of Pathology and Dermatology, Free University Hospital, Amsterdam, the Netherlands
3. Department of Dermatology, University Hospital Groningen, the Netherlands
4. Department of Dermatology, University Hospital Rotterdam, the Netherlands
5. Department of Dermatology, University Hospital Gent, Belgium
6. Department of Dermatology, University Hospital Utrecht, the Netherlands

ABSTRACT

To evaluate our diagnostic and therapeutic guidelines, clinical and long-term follow-up data of 219 patients with primary or secondary cutaneous CD30+ lymphoproliferative disorders were evaluated. The study group included 118 patients with lymphomatoid papulosis (LyP; group 1), 79 patients with primary cutaneous CD30+ large T-cell lymphoma (LTCL; group 2), 11 patients with CD30+ LTCL with skin and regional lymph node involvement (group 3), and 11 patients with secondary cutaneous CD30+ LTCL (group 4). Patients with LyP often did not receive any specific treatment, whereas most patients with primary cutaneous CD30+ LTCL were treated with radiotherapy or excision. All patients with skin-limited disease from groups 1 and 2 who were treated with multiagent chemotherapy had 1 or more skin relapses. The calculated risk for systemic disease within 10 years of diagnosis was 4% for group 1, 16% for group 2, and 20% for group 3 (after initial therapy). Disease-related 5-year-survival rates were 100% (group 1), 96% (group 2), 91% (group 3), and 24% (group 4), respectively. The results confirm the favorable prognoses of these primary cutaneous CD30+ lymphoproliferative disorders and underscore that LyP and primary cutaneous CD30+ lymphomas are closely related conditions. They also indicate that CD30+ LTCL on the skin and in 1 draining lymph node station has a good prognosis similar to that for primary cutaneous CD30+ LTCL without concurrent lymph node involvement. Multiagent chemotherapy is only indicated for patients with full-blown or developing extracutaneous disease; it is never or rarely indicated for patients with skin-limited CD30+ lymphomas.

INTRODUCTION

Primary cutaneous T-cell lymphomas (CTCL) represent a heterogeneous group of neoplasms derived from skin-homing T-cells. Apart from mycosis fungoides (MF), primary cutaneous CD30+ lymphoproliferative disorders are the most common group, accounting for approximately 25% of all CTCL. This group includes primary cutaneous CD30+ (anaplastic) large T-cell lymphomas (LTCL) and lymphomatoid papulosis (LyP), a chronic recurrent, self-healing papulonodular skin eruption with histologic features of a (CD30+) CTCL.[1-3] Because of overlapping clinical, histologic, and immunophenotypical characteristics, these conditions are considered to represent a spectrum of primary cutaneous CD30+ lymphoproliferations.[4,5] It is well established that these primary cutaneous CD30+ lymphoproliferations have favorable prognoses in most patients.[6-12] Previous studies by our group demonstrated significant differences between primary cutaneous CD30+ (anaplastic) LTCL and morphologically similar systemic CD30+ anaplastic large-cell lymphomas.[13] In contrast to these systemic lymphomas, primary cutaneous CD30+ LTCL are rare in children; they generally express the cutaneous lymphocyte antigen (CLA) characteristic of skin-homing T-cells but usually not the epithelial membrane antigen (EMA). They are not associated with Epstein-Barr virus or, according to most studies,[14-17] with the t(2;5) translocation (ALK/p80-negative), and they

have a significantly better prognosis. For these reasons, primary CD30+ CTCL is included as a separate group in the revised European-American classification for non-Hodgkin lymphomas (REAL classification)[18] and in the proposed World Health Organization classification.[19] Notwithstanding the many publications describing the characteristic features of these primary cutaneous CD30+ lymphomas and emphasizing their favorable prognosis, referral centers for cutaneous lymphomas are confronted regularly with patients who have been misdiagnosed or who have been treated with unnecessarily aggressive treatment regimens.[20-22] In particular, the diagnosis LyP is often overlooked. Based on the histologic diagnosis of a CD30+ (anaplastic) LTCL and the presence of multifocal skin lesions, patients with LyP are routinely treated with multiagent chemotherapy by physicians unaware of the spectrum of LyP. Unfortunately, skin relapses during or shortly after systemic chemotherapy are almost the rule and give the false impression of a highly aggressive T-cell lymphoma requiring even more aggressive therapy.

The current report describes the results of a recent evaluation of 219 patients with cutaneous CD30+ lymphoproliferation who were included in the Dutch registry for cutaneous lymphomas between 1983 and 1998. This study was conducted to evaluate our current diagnostic and therapeutic approaches for these patients and to define potential risk factors for tumor progression. Detailed clinical and long-term follow-up data of well-defined groups of primary and secondary cutaneous CD30+ lymphoproliferations are presented. Based on these data, practical guidelines for proper diagnosis, management, and treatment are presented.

Patients and methods

Patients

Between 1983 and 1998, 247 patients with primary or secondary cutaneous CD30+ lymphoproliferation had been included in the database of the Dutch Cutaneous Lymphoma group. Patients with a follow-up less than 12 months unless they died of lymphoma (n = 14), patients with a CD30+ LTCL originating from MF (n = 8), and patients with HIV-associated (n = 4) or posttransplant (n = 2) CD30+ LTCL were excluded. The final study group contained 219 patients, including 118 patients with LyP, 79 patients with primary cutaneous CD30+ LTCL, and 22 patients with cutaneous CD30+ (anaplastic) LTCL with concurrent or prior extracutaneous disease at the time of presentation. Of this latter group, 11 of 22 patients with skin lesions and regional lymph node involvement restricted to 1 site were evaluated as a separate group. All diagnoses were based on combinations of clinical, histologic, and immunohistochemical criteria[23] and were made by an expert panel of dermatologists and hematopathologists at the time of diagnosis, before entry in the database. Because correct categorization (ie, diagnosis) of these lymphomas was crucial, these diagnostic criteria have been summarized in **Table 1**. It should be emphasized that, because of the histologic similarities between LyP and other types of CTCL (MF or CD30+ ALCL), the presence of a recurrent,

self-healing papular or papulonodular eruption is used as a decisive criterion for the diagnosis of LyP. For all patients in groups 2, 3, and 4 and for all patients with LyP type C (TABLE 1), adequate staging procedures including physical examination, routine examination of blood morphology and blood chemistry, radiography of the chest, and computerized tomography of the thorax (most patients) and abdomen were conducted, and bone marrow biopsies were taken. No extracutaneous disease was found in groups 1 and 2. In most other patients with LyP, staging procedures other than physical examination and routine blood examination were not performed.

Follow-up data had been collected yearly for each patient and could therefore easily be retrieved from the database. If necessary, additional information was obtained from the referring physician or from the patient.

Risk factors for tumor progression

As endpoints of tumor progression, extracutaneous disease in patients who initially only had cutaneous disease (groups 1 and 2) and lymphoma-related death were selected. As potential risk factors, the following parameters were scored for each patient: age at diagnosis, sex, morphology, localization and extent of skin lesions (solitary or localized vs multifocal skin lesions), type and result of initial treatment, occurrence and site of relapse (cutaneous or extracutaneous), disease-free survival, and histologic subtype (type A vs type B vs type C in LyP; anaplastic vs nonanaplastic morphology in the other 3 groups). Definitions of the different histologic subgroups have been published previously[5,23] and are summarized in TABLE 1.

Table 1. Diagnostic criteria and histologic subgroups

Category	Diagnostic criteria	Histologic subtype
Group 1 Lymphomatoid papulosis (n = 118)	► Recurrent, self-healing papulonodular eruption. ► Note: spontaneous complete remission of *every individual skin lesion,* irrespective of the appearance of new lesions. ► Histologic features suggesting (CD30+) CTCL.	LyP, type A: (n = 93) LyP, type B: (n = 6) LyP, type C: (n = 8) LyP, mixed (A, B, or both): (n = 11)
Group 2 Primary cutaneous CD30+ large T-cell lymphoma (n = 79)	► Most (>75%) or large clusters of neoplastic cells express the CD30 antigen and have a T- or null cell phenotype ► No clinical evidence of LyP ► No prior or concurrent LyP, MF, or other type of (cutaneous) lymphoma ► No extracutaneous localizations at the time of diagnosis, as assessed with adequate staging.	Anaplastic ► Diffuse (n = 55) ► LyP-like (n = 10) Nonanaplastic ► Pleomorphic (n = 12) ► Immunoblastic (n = 2)
Group 3 CD30+ LTCL presenting with skin lesions and 1 involved regional lymph node station (n = 11)	► Selection criteria of group 2 ► Histologically confirmed involvement of 1 regional lymph node station.	Anaplastic ► Diffuse (n = 8) ► LyP-like (n = 1) Nonanaplastic ► Pleomorphic (n = 2)
Group 4 Secondary cutaneous CD30+ large T-cell lymphoma (n = 11)	► CD30+ (anaplastic) LTCL ► Patients with concurrent cutaneous and extracutaneous disease (other than 1 regional lymph node) (n = 7) or ► Systemic CD30+ (anaplastic) LTCL developing specific skin lesions during follow-up (n = 4)	Anaplastic ► Diffuse (n = 8) Nonanaplastic ► Pleomorphic (n = 3)

LyP, type A: scattered CD30+ blast cells in an extensive inflammatory infiltrate.
LyP, type B: mycosis fungoides-like histology with atypical CD30− T cells with cerebriform nuclei.
LyP, type C: large clusters of CD30+ cells with few inflammatory cells, histologically suggesting a CD30+ (anaplastic) large cell lymphoma.
LyP-like: anaplastic large T-cell lymphomas with relatively few CD30+ tumor cells in an extensive inflammatory infiltrate, histologically suggesting LyP.

Table 2. Main clinical findings and follow-up data

	LyP	Primary cutaneous CD30+ LTCL	CD30+ LTCL in skin and regional lymph nodes	Secondary cutaneous CD30+ LTCL
Number	118	79	11	11
Sex (M:F)	69:49	59:20	4:7	6:5
Age (y)				
Median	45.5	60	64	55
Range	4-88	16-89	27-74	7-87
Extent of skin lesions				
Solitary	0	42 (53%)	7 (64%)	1 (9%)
Regional	15 (13%)	20 (25%)	3 (27%)	1 (9%)
Generalized	103 (87%)	17 (22%)	1 (9%)	8 (82%)
Type of skin lesions				
Papule	80 (68%)	6 (7%)	1 (9%)	3 (27%)
Nodule	4 (3%)	23 (29%)	0	5 (46%)
Papules and nodules	26 (22%)	0	0	0
Tumor	5 (4%)	47 (60%)	10 (91%)	3 (27%)
Plaques	3 (3%)	3 (4%)	0	0
Spontaneous remission				
Absent	0	46 (58%)	8 (73%)	6 (55%)
Partial	0	17 (22%)	1 (9%)	5 (45%)
Complete	118 (100%)	16 (20%)	2 (18%)	0
B symptoms at diagnosis				
Absent	118 (100%)	79 (100%)	11 (100%)	5 (45%)
Present	0	0	0	6 (55%)
Initial therapy				
Radiotherapy	5 (4%)	38 (48%)	0	2 (18%)
Multiagent chemotherapy	0	6 (8%)	9 (82%)	9 (82%)
Excision	0	15 (19%)	1 (9%)	0
PUVA/UV-B	41 (35%)	3 (4%)	0	0
Other	6 (5%)	2 (2%)	0	0
None/topical steroids	66 (56%)	15 (19%)	1 (9%)	0
Result of initial therapy				
Complete remission	16 (14%)	78 (99%)	10 (91%)	3 (27%)
Partial remission	31 (26%)	1 (1%)	0	5 (55%)
No response	61 (60%)	0	1 (9%)	3 (27%)
Disease-free survival (mo)				
Median	NR	23	38	0
Range	NR	1-192	0-84	0-115
Relapse				
Skin *only*	111 (94%)	32 (41%)	4 (36%)	2 (18%)
Regional lymph node	5 (4%)	5 (6%)	1 (9%)	1 (9%)
Systemic	2 (2%)	3 (4%)	1 (9%)	55%
Follow-up (mo)				
Median	77	61	58	22
Range	12-350	13-288	15-284	6-133
Current status				
No evidence of disease	38 (32%)	51 (65%)	6 (55%)	2 (18%)
Alive with disease	73 (62%)	13 (16%)	3 (27%)	1 (9%)
Died of lymphoma	2 (2%)	4 (5%)	1 (9%)	8 (73%)
Died of other cause	5 (4%)	11 (14%)	1 (9%)	0
Disease-related survival				
5 years	100%	96%	91%	24%* (44%)
10 years	100%	96%	91%	24%* (24%)
Overall survival				
5 years	98%	83%	76%	24%* (44%)
10 years	95%	78%	76%	24%* (24%)
Calculated risk for extra-cutaneous disease				
5 years	2%	9%	20%†	80%†
10 years	4%	16%	20%†	80%†

LTCL, large T-cell lymphoma; NR, not relevant.
*Denotes survival after the development of specific skin lesions; percentages between brackets indicate survival after initial diagnosis.
†Denotes risk of *new* extracutaneous disease (either progression or relapse) after initial therapy.

Statistical analysis

As indicators of survival, both disease-specific survival (including only death related to lymphoma as event) and overall survival (including death related to any cause as event) were investigated. Actuarial survival curves were calculated from the date of diagnosis to the date of death or last contact using the Kaplan-Meier technique. Univariate analysis of possible risk factors for tumor progression was performed using log-rank test and Cox proportional hazards regression analysis. Multivariate analysis was performed using significant univariate variables from Cox proportional hazards regression analysis. All analyses were performed with the SPSS statistic software (SPSS, Chicago, IL).

RESULTS

The main clinical characteristics for the 4 groups studied are summarized in TABLE 2. Additional information for these groups is given separately below.

Lymphomatoid papulosis

Group 1 consisted of 69 males and 49 females with a median age of 45.5 years at diagnosis (range, 4 to 88 years). Patients initially sought treatment for papular, papulonecrotic, or nodular skin lesions, and 8 patients (7%) also sought it for additional plaques or tumors. Characteristically, skin lesions in different stages of evolution were found next to each another (FIGURE 1). There was no preferential anatomic site of involvement. The group included 12 patients (10%) younger than 20 years of age at the

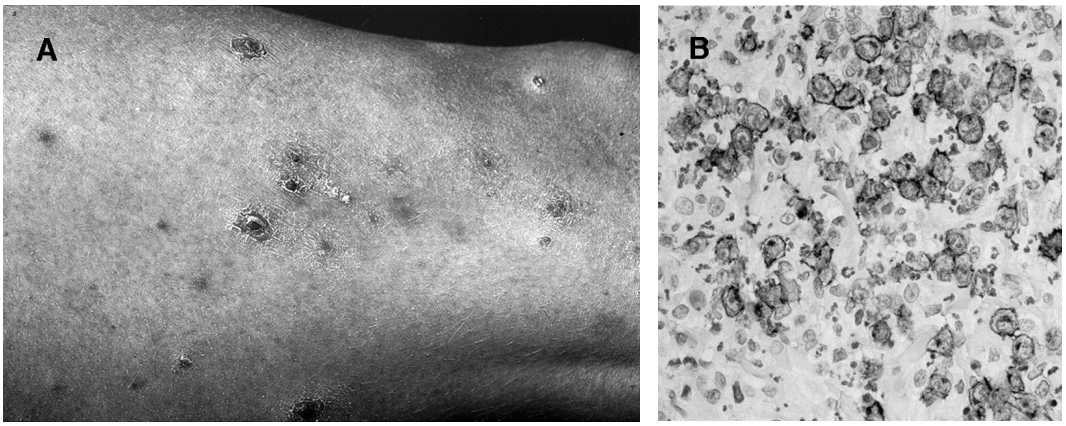


FIGURE 1. Lymphomatoid papulosis. (A) Characteristic papular and papulonecrotic lesions at different stages of evolution. (B) Mixed inflammatory infiltrate with scattered CD30

time of diagnosis (median, 12 years; range, 4 to 19 years). Interestingly, 3 of these children (6, 13, and 16 years of age) had papules and rapidly growing ulcerating nodules or tumors. Despite this alarming clinical presentation, the lesions slowly subsided within 6 to 10 weeks without any specific treatment. None of the 12 children had extracutaneous disease or died of lymphoma after a median follow-up of 52 months (range, 25 to 131 months).

Throughout the course of their disease, 52 of 118 patients received no therapy other than topical steroids, which was not always recorded. Therapies most commonly applied in the other patients included psoralen-UV-A (PUVA) or UV-B phototherapy or chemotherapy (46 patients), topical nitrogen mustard (8 patients), and low doses of methotrexate (8 patients). Although partial or even complete remission was common, none of these therapies resulted in sustained complete remission. Similarly, remission after systemic chemotherapy or total skin electron beam irradiation, given for associated malignancies, was short-lived and did not affect the natural course of LyP. Associated lymphomas, either before, after, or concurrently with the development of LyP, were observed in 23 of 118 (19%) patients (**TABLE 3**). One of these 23 patients had systemic CD30+ ALCL, which went into complete remission after multiagent chemotherapy, 6 years before LyP developed. Eleven of these 23 patients had concurrent LyP and MF. The diseases ran indolent clinical courses in all these patients. Large, persistent tumors developed in 4 patients with LyP; they were treated with radiotherapy (2 patients) or disappeared spontaneously (2 patients) (**FIGURE 2**). Extracutaneous disease developed in only 7 of 118 patients. Skin tumors with involved regional lymph nodes developed in 4 of these 7 patients. Although 2 of these 4 patients were treated with cyclophosphamide-doxorubicin-vincristine-prednisone (CHOP) courses, skin and lymph node localizations disappeared spontaneously in the other 2 patients, and planned chemotherapy was not given. Systemic lymphoma developed in the other 3 of those 7 patients (CD30+ LTCL with lung localization in 1 patient and Hodgkin disease in 2 patients). All 3 patients were treated with

Table 3. Associated lymphomas in patients with lymphomatoid papulosis

Patient	Sex/age (y)	Associated lymphoma	Time interval* (y)	Localization		Therapy	Current status (follow-up in mo)	
				Skin	ec		Lymphoma	LyP
1	F/48	CD30+ LTCL	B (5)	–	+	RT	A^0 (120)	A^+ (57)
2	M/46	CD30+ LTCL	A (1)	+	–	RT	A^0 (81)	A^+ (94)
3	M/28	CD30+ LTCL	A (25, 27)	+	–	RT/None†	A^0 (50, 20)	A^+ (350)
4	F/24	CD30+ LTCL	A (2, 3)	+	–	None†	A^0 (57, 43)	A^+ (77)
5	M/12	CD30+ LTCL	A (1)	+	–	None†	A^0 (4)	A^+ (21)
6	M/23	CD30+ LTCL	A (1)	+	+‡	CHOP	A^0 (144)	A^+ (156)
7	M/31	CD30+ LTCL	A (5)	+	+	CHOP	A^0 (39)	A^+ (99)
8	F/53	CD30+ LTCL	A (1)	+	+‡	None†	A^0 (105)	A^+ (115)
9	M/43	CD30+ LTCL	A (1)	+	+‡	None†	A^0 (14)	A^+ (27)
10	M/52	CD30+ LTCL	A (18)	+	+	CHOP	D^+ (12)	D^+ (228)
11	F/64	Hodgkin disease	A (6)	–	+	MOPP	D^0 (77)	D^0 (142)
12	M/33	Hodgkin disease	A (13)	–	+	MOPP	D^+ (6)	D^+ (168)
13	M/38	Mycosis fungoides (Ib)	A (4)	+	–	PUVA	A^+ (98)	A^+ (142)
14	F/72	Mycosis fungoides (Ib)	B (4)	+	–	RT	A^+ (143)	A^0 (97)
15	F/56	Mycosis fungoides (Ib)	A (10)	+	–	HN_2	A^0 (244)	A^+ (118)
16	M/45	Mycosis fungoides (Ia)	A (4)	+	–	HN_2	A^+ (131)	A^+ (177)
17	F/88	Mycosis fungoides (Ib)	C	+	–	Retinoids + PUVA	D^0 (23)	D^0 (23)
18	M/73	Mycosis Fungoides (Ib)	A (8)	+	–	UVB	A^0 (102)	A^0 (199)
19	F/24	Mycosis Fungoides (Ib)	C	+	–	PUVA	A^+ (94)	A^+ (94)
20	M/59	Mycosis Fungoides (Ib)	A (12)	+	–	TSEB	A^0 (218)	A^+ (77)
21	M/64	Mycosis Fungoides (Ia)	A (2)	+	–	UVB	A^+ (34)	A^+ (55)
22	M/51	Mycosis Fungoides (Ib)	C	+	–	PUVA	A^+ (20)	A^+ (20)
23	M/73	Mycosis Fungoides (Ib)	B (8)	+	–	PUVA	D^0 (160)	D^0 (78)

*Associated lymphoma before (B), after (A), or concurrent (C) with the development of lymphomatoid papulosis.
†Complete spontaneous resolution before initiation therapy.
‡Involved draining lymph node only.
ec, extracutaneous; LyP, lymphomatoid papulosis; CD30+ LTCL, CD30+ large T-cell lymphoma; RT, radiotherapy; A^0, alive no evidence of disease; A^+, alive with disease; D^0, died of unrelated disease; D^+, died of lymphoma; CHOP, cyclophosphamide, doxorubicin, vincristine, prednisone; MOPP, mechlorethamine, vincristine, procarbazine, prednisone; HN_2, topical nitrogen mustard; TSEB, total skin electron beam irradiation; mycosis fungoides, in all patients patch/plaque stage MF affecting <10% (Ia) or >10% (Ib) of the skin surface.

multiagent chemotherapy. After a median follow-up of 77 months (range, 12 to 350 months), 111 patients (94%) are alive, 5 patients (4%) died of nonrelated disease, and only 2 patients (2%) died of systemic CD30+ LTCL or Hodgkin disease 14 and 19 years, respectively, after the diagnosis of LyP. Both patients have been described in more detail.[24,25]

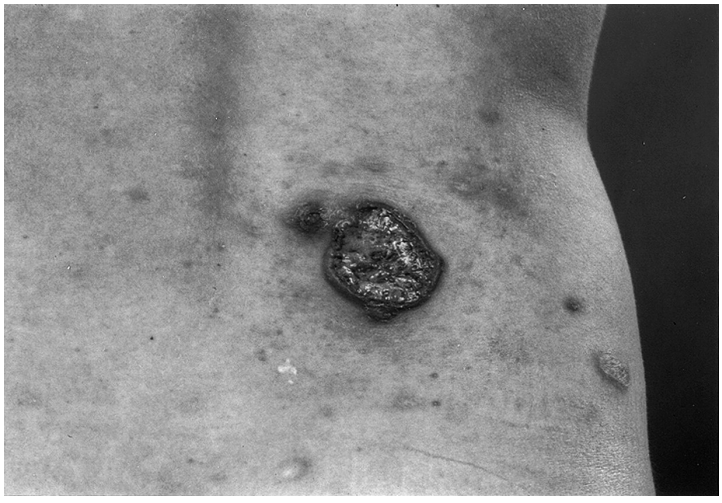


FIGURE 2. A large ulcerating tumor (diameter, 5 cm) developed in a 12-year-old boy with lymphomatoid papulosis. The tumor disappeared spontaneously within 2 months.

Evaluation of risk factors for tumor progression by univariate analysis did not reveal statistically significant results ($P > 0.1$), which may be explained by the small proportion (4%) of patients with LyP in whom extracutaneous disease developed. Notably, none of the 8 patients with LyP whose skin biopsies revealed cohesive sheets of

CD30+ cells (LyP type C) died of lymphoma. In addition, after a follow-up of 23 to 156 months (median, 43 months), extracutaneous disease developed in only 1 (FIGURE 3).

Primary cutaneous CD30+ large cell lymphoma

Group 2 consisted of 59 males and 20 females with a median age of 60 years at diagnosis (range, 16 to 89 years). Only 1 patient was younger than 20 years of age, illustrating that there is no bimodal age distribution in this group. Patients usually sought treatment for a solitary (ulcerating) tumor (42 patients) or several grouped nodules or papules restricted to 1 skin area (20 patients) (FIGURE 4). Only 17 patients (22%) had multifocal skin disease, ie 2 (n = 9) or more (n = 8) lesions at multiple anatomic sites (FIGURE 5). Partial or even complete spontaneous remission of skin lesions, either at diagnosis or at relapse, were observed in 33 (42%) patients.

Initial treatment consisted of radiotherapy (47%) or surgical excision (22%). Only 6 patients (8%) received doxorubicin-based multiagent chemotherapy, including 4 of 17 patients who sought treatment for multifocal skin lesions. Twelve patients (15%) received no treatment because of spontaneous, complete remission of the skin lesions. Although 33 of 79 patients (42%) had 1 or more skin relapses, extracutaneous disease developed in only 8 of 79 patients (10%). Treatment consisted of CHOP courses (6 patients) or autologous bone marrow transplantation. After a median follow-up of 61 months (range, 13 to 288 months), only 4 patients died of lymphoma.

Patients with multifocal skin lesions more often acquired extracutaneous disease (17% vs 8%) and more often died of lymphoma (12% vs 3%) than patients with solitary or localized skin lesions. However, univariate analysis demonstrated that neither extent of skin lesions, age at diagnosis, presence of spontaneous remission, histologic subtype, or any other variable tested was significantly related to disease progression or survival. Multivariate analysis, therefore, was not performed.

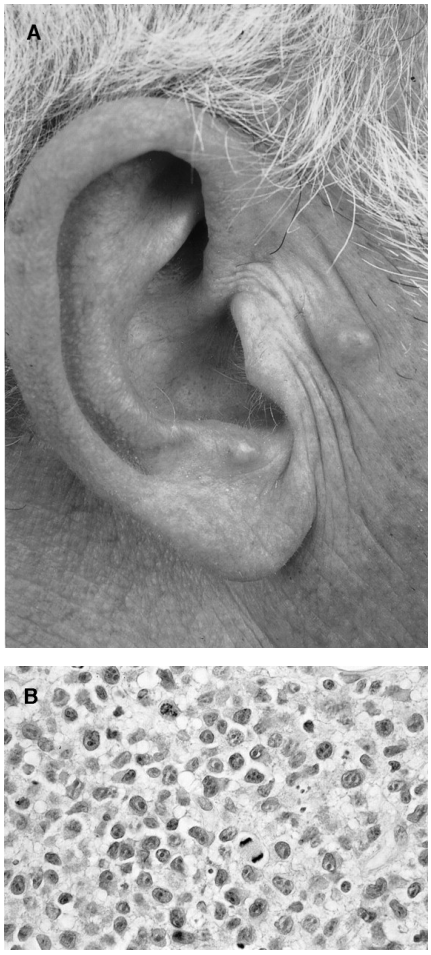
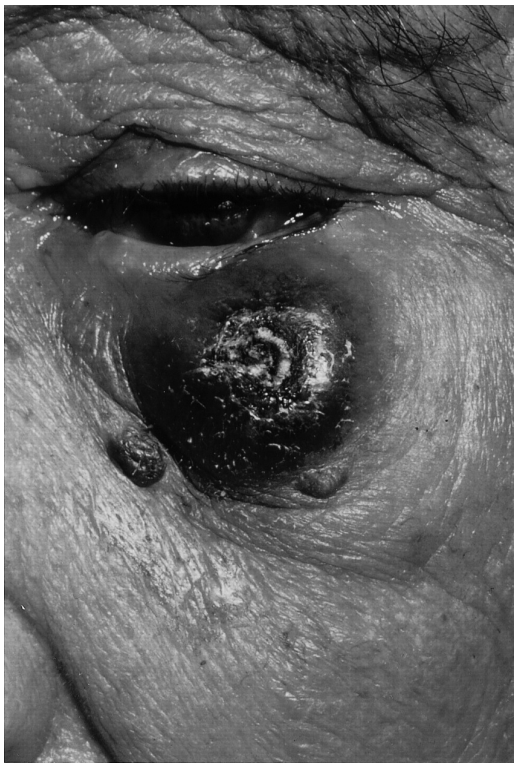
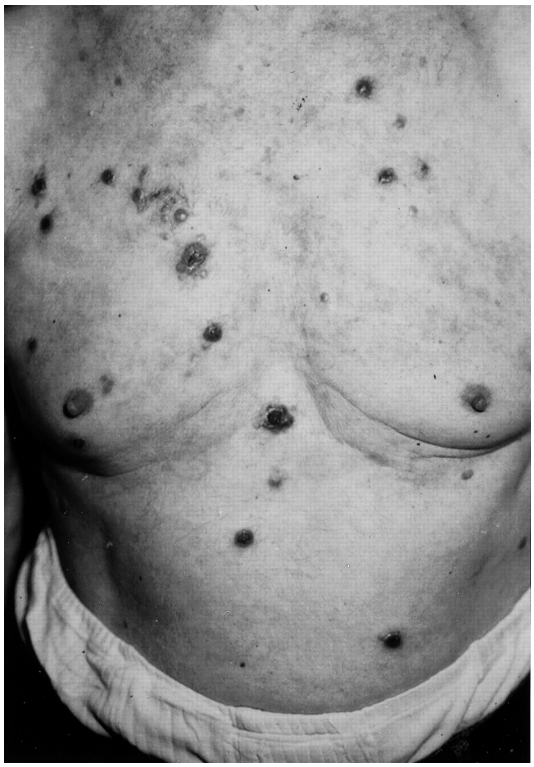


FIGURE 3. Lymphomatoid papulosis (type C). (A) Approximately 10 firm papules on the face and the chest. (B) Detail of dermal infiltrate showing a monotonous population of large anaplastic (CD30





LEFT:
FIGURE 4. Primary cutaneous CD30

RIGHT:
FIGURE 5. Primary cutaneous CD30

CD30+ LTCL with skin and draining lymph node involvement

Group 3 consisted of 4 men and 7 women with a median age of 64 years (range, 27 to 74 years). Ten of 11 patients had 1 (8 patients) or several (2 patients) ulcerating tumors in 1 anatomic area and enlarged, histologically involved draining lymph nodes at that site. Initial therapy consisted of CHOP-like multiagent chemotherapy in 9 of 11 patients (82%) and resulted in complete remission in 8 of them. However, 5 of these 8 patients had skin relapses during follow-up. In 2 other patients not treated with systemic chemotherapy, skin and nodal lesions disappeared spontaneously after diagnostic excision of the skin tumor, and no further treatment was instituted. Neither of them had a relapse, and both are still in complete remission 24 and 79 months after diagnosis, respectively. After a median follow-up of 58 months (range, 15 to 248 months), 9 patients are alive, 1 died of unrelated disease, and 1 died of lymphoma. The disease-related 5-year survival rate in this group was 91% (**FIGURE 6**).

Secondary cutaneous CD30+ large T-cell lymphoma

Group 4 consisted of 6 males and 5 females with a median age of 55 years (range, 7 to 87 years). Seven patients had extensive cutaneous and extracutaneous disease. The age distribution was typically bimodal: 3 patients were younger than 22 years and 4 were older

than 55 years. Treatment with multiagent chemotherapy resulted in complete remission in only 2 of 7 patients; 6 of these 7 patients died after a median period of only 13 months (range, 6 to 46 months). The remaining patient is alive and well more than 10 years after autologous bone marrow transplantation.

Skin lesions developed in the other 4 patients 5 to 108 months (median, 53 months) after the diagnosis of systemic CD30+ ALCL was made. The ages of these patients (15, 24, 60, and 70 years) also suggested a bimodal age distribution. Treatment consisted of multiagent chemotherapy (3 patients) or radiotherapy at multiple sites (1 patient). Only 1 of 4 patients achieved complete remission. Two patients died 10 and 26 months after the development of skin lesions (63 and 132 months after initial diagnosis), the other 2 are alive 43 and 131 months after the development of skin lesions (48 and 185 months after initial diagnosis).

Discussion

In the current study, clinical and histologic variables of a major group of 219 cutaneous CD30+ lymphoproliferations were evaluated. The primary goals of this analysis were a critical evaluation of our current diagnostic and therapeutic approaches and a definition of potential risk factors for tumor progression. Relevant features of the different groups of cutaneous CD30+ lymphomas are discussed, and guidelines for correct diagnosis and treatment are presented.

Primary cutaneous CD30+ large T-cell lymphoma

Primary cutaneous CD30+ LTCL predominantly affected adults but rarely affected children (see below). They generally appeared as solitary or localized skin lesions (78%), they had the tendency to regress spontaneously, they frequently relapsed on the skin (41%) but uncommonly disseminated to extracutaneous sites (10%), and their prognosis was excellent with 5- and 10-year disease-related survival rates exceeding 95%. These findings confirm and extend the results of previous studies on smaller groups of patients.[5-11]

Risk factors predicting tumor progression or dissemination could not be found. This may be related to the small number of patients in whom extracutaneous disease developed (8 of 79 patients) and the small number of tumor-related deaths (4 of 79 patients). No differences in survival rates for patients with lymphoma with or without typical anaplastic morphology were found. However, CD30+ LTCL with an LyP-like histology (few CD30+ cells) more often showed complete spontaneous remission (50%) than CD30+ LTCL with large clusters of CD30+ anaplastic (29%) or nonanaplastic cells (28%). Neither extent of skin lesions (solitary or localized vs multifocal skin lesions) nor age was significantly related to survival.

Interestingly, the group of patients with CD30+ LTCL with skin lesions and only 1 involved draining lymph node station (group 3) had the same clinical features (presentation with solitary or localized skin lesions, no bimodal age distribution, good response to therapy) and a similarly good prognosis as the group with primary cutaneous CD30+ LTCL. Recent studies demonstrated that systemic CD30+ anaplastic large-cell lymphomas expressing ALK have a much better prognosis than ALK-negative lymphomas (5-year survival rates, 93% vs 37%).[26] Immunohistochemical studies of 5 patients in group 3 demonstrated an ALK, EMA, CLA+ immunophenotype in each of them. As a comparison, the results of ALK staining in 28 other patients showed a positive reaction in 3 of 4 patients with secondary cutaneous CD30+ LTCL but not in 15 patients with primary cutaneous CD30+ LTCL, and they showed neither in 9 patients with LyP.[17] The favorable prognosis for our group 3 patients cannot simply be attributed to the fact that 9 of 11 patients were treated with systemic chemotherapy. If this were representative of skin localizations of an ALK-negative systemic lymphoma, a less favorable outcome would have been expected for this group. Our clinical and immunohistochemical observations suggest rather that these patients are in fact patients with primary cutaneous

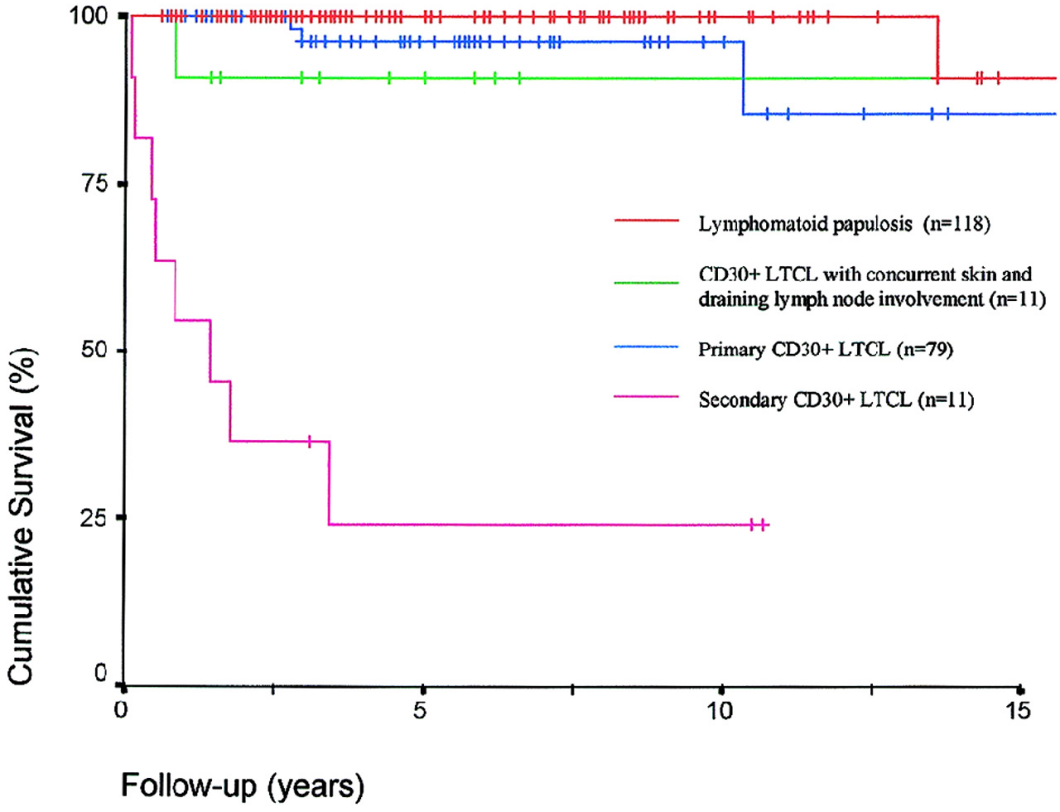


FIGURE 6. Survival curve of different groups of primary and secondary cutaneous CD30

CD30+ LTCL with (early) dissemination to the regional lymph nodes.

Major differences were found between the above-mentioned groups and patients with systemic CD30+ anaplastic large T-cell lymphomas with concurrent or secondary skin involvement. These patients more often sought treatment for generalized skin lesions. They had a bimodal age distribution, poor responses to often intensive treatment, and poor prognoses, with 5-year-survival rates of 44% after diagnosis and 23% after the development of skin lesionssuggesting that the appearance of skin lesions in CD30+ ALCL is a poor prognostic sign.[11]

Therapy

In patients with a solitary or few localized nodules or tumors, local radiotherapy is the first choice of treatment. However, follow-up data indicate that if the lesion has been excised completely or has disappeared spontaneously, no further therapy is required. If a skin lesion relapses, spontaneous resolution can be awaited for some weeks or the patient can undergo radiotherapy or surgical excision. According to our existing guidelines formulated in 1991, patients with multifocal skin lesions should be treated with doxorubicin-based multiagent chemotherapy. However, only 7 of 17 patients with multifocal skin lesions in this study had ever been treated with systemic chemotherapy. More important, all patients who were treated with CHOP courses because of multifocal skin lesions (6 of 7 patients) had 1 or several skin relapses afterward. Moreover, in 3 of these 17 patients, all initial skin lesions disappeared spontaneously. Unlike LyP lesions, however, relapse did not occur during the 32- to 72-month follow-up. These observations suggest that multifocal skin-restricted CD30+ LTCL should not be treated routinely with multiagent chemotherapy. If spontaneous regression does not occur, these patients can best be treated with radiotherapy for a few lesions or with low-dose methotrexate as for LyP.[20,27] In patients with full-blown or developing regional lymph node involvement, multiagent chemotherapy is still considered the safest option. However, skin relapses after chemotherapy are common, but they are not associated with an aggressive clinical behavior and therefore do not require an aggressive approach. Moreover, complete spontaneous resolution of skin and lymph node localizations may occur. In such patients an expectative approach seems justified.

Lymphomatoid papulosis

In this very large group of patients with LyP with a median follow-up of 77 months and of 29 patients with a follow-up of more than 10 years, 23 of 118 patients (19%) had associated malignant lymphoma either before, after, or concurrent with LyP. However, only 7 of 118 had extracutaneous disease, and only 2 of 118 patients died of systemic lymphoma. The calculated risk for systemic lymphoma within the first 10 or 15 years after diagnosis was 4% and 12%,

respectively, in contrast with the 80% at 15 years in a study of Cabanillas et al.[21] However, in that study, only patients with LyP who had initially been misdiagnosed or had another type of malignant lymphoma were included, suggesting that the striking difference between both studies results from differences in patient selection. As in earlier studies on smaller groups of patients,[25,28,29] risk factors for disease progression could not be found.

Therapy

Because a curative therapy is unavailable and none of the available treatment modalities affects the natural course of the disease, the short-term benefits of active treatment should be balanced carefully against the potential side effects.[5,20] We believe that in patients with relatively few and nonscarring lesions, active treatment is not necessary. In patients with cosmetically disturbing lesions (eg, scarring lesions or many lesions), low-dose oral methotrexate (5 to 20 mg/wk) or PUVA therapy can be administered to reduce skin lesions.[20,27,30] When larger skin tumors develop in the course of LyP, spontaneous remission can be awaited for 4 to 6 weeks. If spontaneous resolution does not occur, such lesions can be excised or treated with radiotherapy. Whether such isolated skin tumors developing in the course of LyP should be considered progression to CD30+ LTCL is debatable.

Primary cutaneous CD30+ lymphoproliferations in children

Of the 12 children with LyP in this study, 3 had large, rapidly growing ulcerating lesions in addition to papular lesions. Because of this distressing clinical presentation suggesting aggressive lymphoma, multiagent chemotherapy was first considered in all 3 children. However, because the histologic appearance was highly suggestive of LyP and staging procedures did not show any evidence of extracutaneous disease, it was decided to wait for several weeks. In all 3 patients the larger skin lesions disappeared completely within 2 to 3 months, whereas the papular lesions continued to develop. This illustrates that the physician should be cautious before using aggressive chemotherapy to treat children with skin-limited CD30+ lymphoproliferations because they often simply have LyP (12 of 13 patients younger than 20 in this study). A short period of watchful waiting is warranted and may avert unnecessary treatment. Previous studies also report an indolent course for children with LyP.[28,31,32]

Guidelines for diagnosis, management, and treatment

The central problem in the correct diagnosis and classification of this group of diseases is that there are no reliable histologic criteria to differentiate between the different types of primary and secondary cutaneous CD30+ lymphoproliferations. Patients with cutaneous CD30+ LTCL may show an LyP-like histology, whereas patients with the characteristic clinical presentation and clinical behavior of LyP may show large sheets of CD30+ cells with only few infiltrating reactive cells (LyP, type C). Consequently, the histologic diagnosis

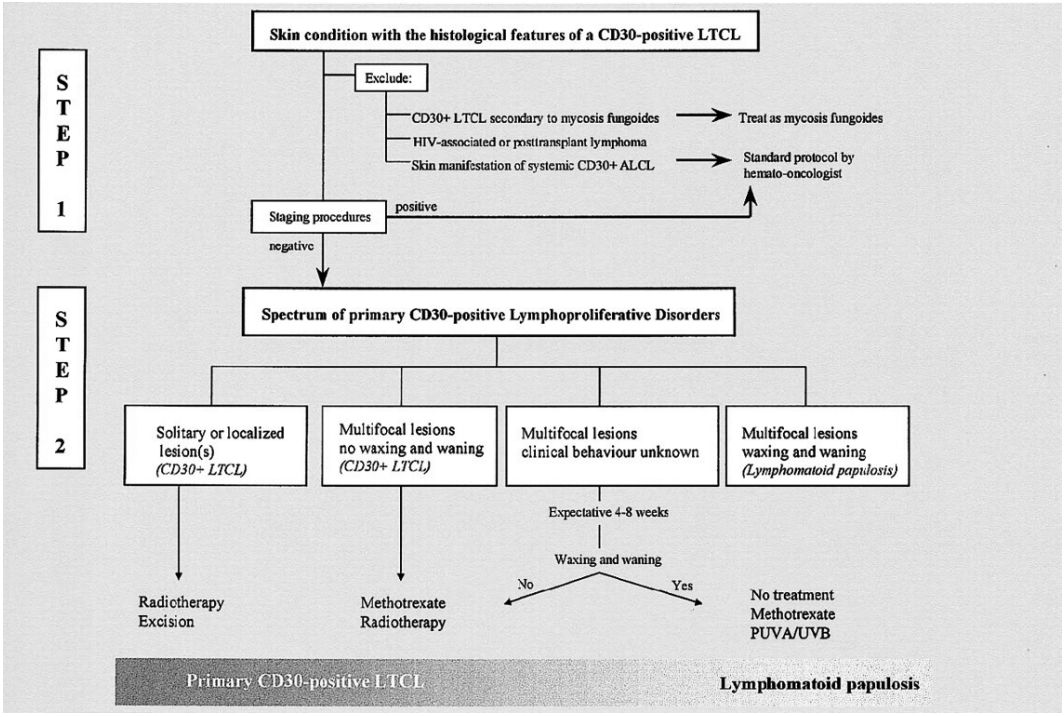


FIGURE 7. Algorithm for the diagnosis and treatment of cutaneous CD30

should always be considered as a differential diagnosis and should never serve as a basis for therapeutic decisions. The definite diagnosis should always be based on a combination of histological and clinical criteria. This diagnostic process involves 2 steps (**FIGURE 7**). The first and most important question is whether it is a primary or a secondary cutaneous CD30+ lymphoproliferation. The second question is whether it is LyP or primary cutaneous CD30+ LTCL.

Step 1: primary or secondary cutaneous CD30+ lymphoma?

Confronted with a patient with the histologic diagnosis of a cutaneous CD30+ lymphoproliferation, distinctions should first be made among primary cutaneous CD30+ lymphoproliferation, cutaneous CD30+ lymphoma secondary to MF (or another type of CTCL), and skin localizations of a systemic CD30+ (anaplastic) LTCL. Cutaneous CD30+ lymphomas secondary to MF can generally be recognized easily because of the presence of prior or concurrent patches or plaques with the typical histology of MF. If no extracutaneous disease can be demonstrated, patients can be treated routinely as for tumor-stage MF, primarily with skin-directed therapies such as local radiotherapy or total skin electron beam irradiation. Patients with skin and extracutaneous localizations require multiagent chemotherapy and generally have an unfavorable prognosis. MF with transformation into a

CD30+ LTCL should not be confused with MF with concurrent LyP, a combination observed in 9% of patients with LyP (current study) and in approximately 3% of patients with MF[33] and carrying, almost without exception, a very good prognosis.[25,33,34]

To exclude secondary cutaneous CD30+ (anaplastic) LTCL, we suggest adequate staging in all patients with cutaneous CD30+ lymphoproliferation. An exception is made for patients with clinical and histologic features characteristic of LyP in whom meticulous physical examination suffices.[20]

Step 2: management of primary cutaneous CD30+ lymphoproliferations.
Previous studies emphasize the many similarities between primary cutaneous CD30+ LTCL and LyP, suggesting that these are closely related conditions within a continuous spectrum.[4,5] Distinction between these 2 ends of the spectrum was considered important because patients with CD30+ LTCL were thought to be at much higher risk for extracutaneous disease than patients with LyP and, unlike patients with LyP, always required adequate staging and even systemic chemotherapy if they had multifocal skin lesions.[5,11] However, the results of the current study suggest that the differences in disease progression and survival between both groups are smaller than anticipated previously (**TABLE 2**). In addition, skin relapses after systemic chemotherapy were not only observed in patients with LyP but also in all patients with skin-limited CD30+ LTCL,[22] which argues against the use of systemic chemotherapy for patients with only skin lesions. Taken together, our observations indicate that the choice of treatment should be based above all on the size, the extent, and the clinical behavior of the skin lesions and not as much on the diagnosis of CD30+ LTCL or LyP (**FIGURE 6**).

Following this approach, distinction is first made between patients with a solitary or few localized nodules or tumors and patients with multifocal skin lesions. The term localized refers to a few clustered lesions restricted to 1 anatomic area generally not exceeding 15 × 15 cm. These primary cutaneous CD30+ LTCL may show spontaneous resolution, either partial or complete, but they do not wax and wane as do LyP lesions. As discussed before, local radiotherapy is the first choice of treatment. Most patients with multifocal skin lesions have LyP. Characteristically, skin lesions wax and wane, and skin lesions coexist in different stages of evolution. These include early small red papules, fully developed papules or nodules with or without central ulceration, brown-red disappearing lesions, residual lesions, and sometimes residual scars. Complete disappearance of every single lesion, irrespective of the appearance of new lesions, is a prerequisite. Most patients do not require any specific treatment. If a patient has cosmetically disturbing lesions, low-dose oral methotrexate (5 to 20 mg/wk) or PUVA therapy may be considered. Multifocal skin lesions that do not wax and wane as in LyP are less common. Nevertheless, skin lesions in these multifocal primary cutaneous CD30+

LTCL may also show partial, and sometimes even complete, spontaneous remission, which can often be recognized clinically by the skin lesions turning from red to brown. As discussed before, patients with such lesions should no longer be treated routinely with doxorubicin-based multiagent chemotherapy because skin relapses after chemotherapy are likely to occur. If spontaneous remission does not occur, radiotherapy or low-dose methrotrexate is the best treatment if there are only a few lesions.

In some patients with a brief history of multifocal skin lesions, the clinical behavior may still be unknown, and a definite diagnosis cannot yet be made. It is our experience in particular that such patientsnot uncommonly colleagues or close relatives are often treated with systemic chemotherapy. However, because extracutaneous disease has already been excluded, and because not only LyP but also primary cutaneous CD30+ LTCL has a low tendency to progress to extracutaneous disease, it is better to wait for several weeks while monitoring closely the natural evolution of the skin lesions. After a period of 4 to 8 weeks, a definite diagnosis can normally be made, and the appropriate treatment can then be selected.

In conclusion, the results of this study confirm the indolent clinical behavior and excellent prognosis of a group of primary cutaneous CD30+ lymphoproliferations. Close collaboration between dermatologists, pathologists, and hematologists/oncologists is the best guarantee for a correct diagnosis and proper treatment. If a definite diagnosis cannot yet be made, an expectative approach seems justified. Multiagent chemotherapy is only indicated for patients with existent or developing extracutaneous disease. It is indicated rarely or not at all for patients with only skin lesions. For all patients, however, long-term follow-up is required.

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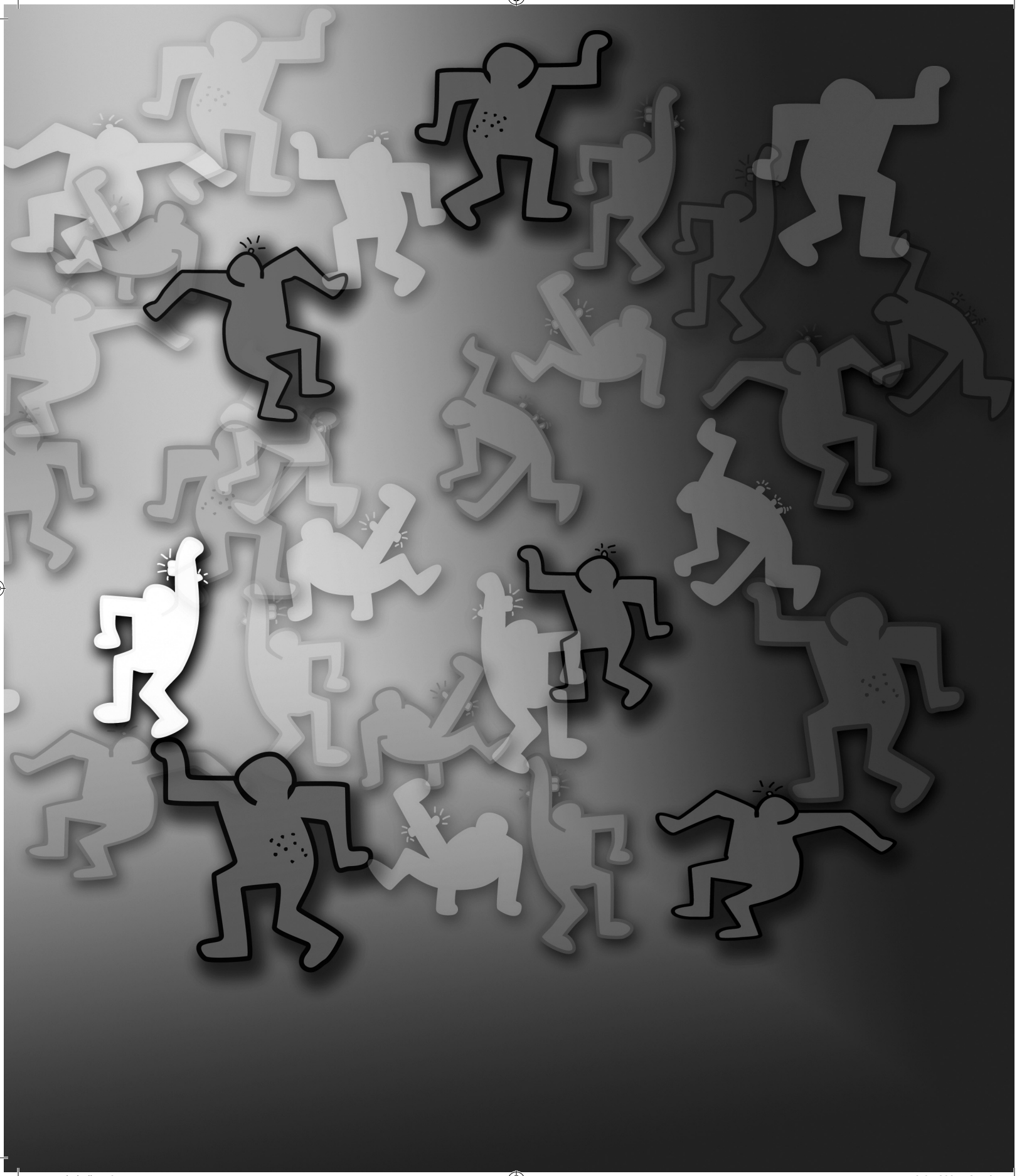

chapter 3

Peripheral T-cell lymphomas unspecified presenting in the skin: analysis of prognostic factors in a group of 82 patients

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Marcel W. Bekkenk [1]
Maarten H. Vermeer [1]
Patty M. Jansen [2]
Ariënne M. W. van Marion [3]
Marijke R. Canninga-van Dijk [3]
Philip M. Kluin [4]
Marie-Louise Geerts [5]
Chris J. L. M. Meijer [6]
Rein Willemze [1]

1. Department of Dermatology, Leiden University Medical Center, Leiden, the Netherlands
2. Department of Pathology, Leiden University Medical Center, Leiden, the Netherlands
3. Department of Pathology, University Medical Center Utrecht, Utrecht, the Netherlands
4. Department of Pathology, University of Groningen, Groningen, the Netherlands
5. Department of Dermatology, University Hospital Gent, Gent, Belgium
6. Department of Pathology, Vrije Universiteit Medical Center, Amsterdam, the Netherlands

Abstract

In the present study the clinicopathologic and immunophenotypic features of 82 patients with a CD30– peripheral T-cell lymphoma, unspecified, presenting in the skin were evaluated. The purpose of this study was to find out whether subdivision of these lymphomas on the basis of cell size, phenotype, or presentation with only skin lesions is clinically relevant. The study group included 46 primary cutaneous CD30– large cell lymphomas and 17 small/medium-sized T-cell lymphomas as well as 17 peripheral T-cell lymphomas with both skin and extracutaneous disease at the time of diagnosis. Patients with primary cutaneous small- or medium-sized T-cell lymphomas had a significantly better prognosis (5-year-overall survival, 45%) than patients with primary cutaneous CD30– large T-cell lymphomas (12%) and patients presenting with concurrent extracutaneous disease (12%). The favorable prognosis in this group with primary cutaneous small- or medium-sized T-cell lymphomas was particularly found in patients presenting with localized skin lesions expressing a CD3+CD4+CD8– phenotype. In the primary cutaneous T-cell lymphoma (CTCL) group and in the concurrent group, neither extent of skin lesions nor phenotype had any effect on survival. Our results indicate that peripheral T-cell lymphomas, unspecified, presenting in the skin have an unfavorable prognosis, irrespective of the presence or absence of extracutaneous disease at the time of diagnosis, cell size, and expression of a CD4+ or CD8+ phenotype. The only exception was a group of primary cutaneous small- or medium-sized pleomorphic CTCLs with a CD3+CD4+CD8– phenotype and presenting with localized skin lesions.

Introduction

Mature or peripheral T-cell or natural killer (NK) cell lymphomas are uncommon, accounting for approximately 12% of all non-Hodgkin lymphomas in the Western world.[1] These peripheral T/NK-cell lymphomas frequently involve the skin, either as primary or as secondary manifestation of the disease. With respect to the primary cutaneous T-cell lymphomas (CTCLs), both in the European Organization for Research and Treatment of Cancer (EORTC) classification for primary cutaneous lymphoma[2] and in the World Health Organization (WHO) classification,[3] mycosis fungoides (MF), Sézary syndrome (SS), the group of the primary cutaneous CD30+ lymphoproliferations, and subcutaneous panniculitis-like T-cell lymphomas are recognized as distinct well-defined entities, which together constitute approximately 85% of all primary CTCLs.[2] In the EORTC classification most cases of primary CTCL that do not belong to one of these entities are included in the group of CD30– large-cell CTCLs and in the provisional group of CD30– small/medium-sized pleomorphic CTCLs. Distinction between the two categories, which is based on the presence of more or less than 30% large neoplastic T-cells, is considered useful because of a significant difference in survival between the groups.[4,5] The EORTC classification does not include cases presenting with prior or concurrent extracutaneous disease, and it does not

make further distinction between cases with a CD4+ T-cell phenotype and those with a CD8+ T-cell phenotype, although recent studies have suggested that epidermotropic CD8+ CTCL with a cytotoxic phenotype should be considered as a distinct disease entity.[6] In the WHO classification most of these CD30– large-cell and small/medium-sized pleomorphic CTCLs are classified as peripheral T-cell lymphomas (PTLs), unspecified, and rare cases as extranodal T/NK-cell lymphoma, nasal-type. In the group of PTLs, unspecified, no further subdivision is made by site of presentation (eg, distinction between primary and secondary cutaneous involvement), cell size, or phenotype.

In ongoing attempts to evaluate the clinical usefulness of the EORTC and WHO classifications, we evaluated the clinicopathologic features of 82 patients with PTL, unspecified, presenting in the skin. The primary goal of this study was to find out whether subdivision of these lymphomas on the basis of cell size, phenotype, or presentation with or without concurrent extracutaneous involvement is clinically and prognostically relevant.

Patients and methods

Patient selection

Between October 1985 and December 1999, a total of 883 patients with skin manifestations of a T/NK-cell lymphoma were included in the registry of the Dutch Cutaneous Lymphoma Group (Figure 1). For this study 3 groups of patients were selected for further evaluation: patients with primary cutaneous CD30– large T-cell lymphoma (n = 49), patients with primary cutaneous CD30– small/medium-sized pleomorphic CTCL (n = 26), and a group of 18 patients with both cutaneous and extracutaneous involvement of a CD30– T-cell lymphoma at the time of first diagnosis. Nine patients with history of a primarily noncutaneous T/NK-cell lymphoma—including 5 patients with a nasal T/NK-cell lymphoma, 3 with an angioimmunoblastic T-cell lymphoma (AITL), and 1 with a nodal PTL, unspecified—who developed specific skin lesions during follow-up were not included in this study.

The 2 groups of primary CTCLs were defined according to the criteria of the EORTC classification.[2] In all cases adequate staging procedures, including physical examination, complete blood cell counts, computed tomography of chest and abdomen, and a bone marrow biopsy, had failed to demonstrate extracutaneous disease at time of diagnosis. The third group of patients, who also presented with skin lesions but after staging appeared to have also extracutaneous disease at the time of first diagnosis, was included to find out whether patients presenting with skin-limited disease had a better prognosis. These cases do not represent primary CTCLs and are not included in the EORTC classification. Following the criteria of the WHO classification, all 93 patients were classified as having PTL, unspecified.[3]

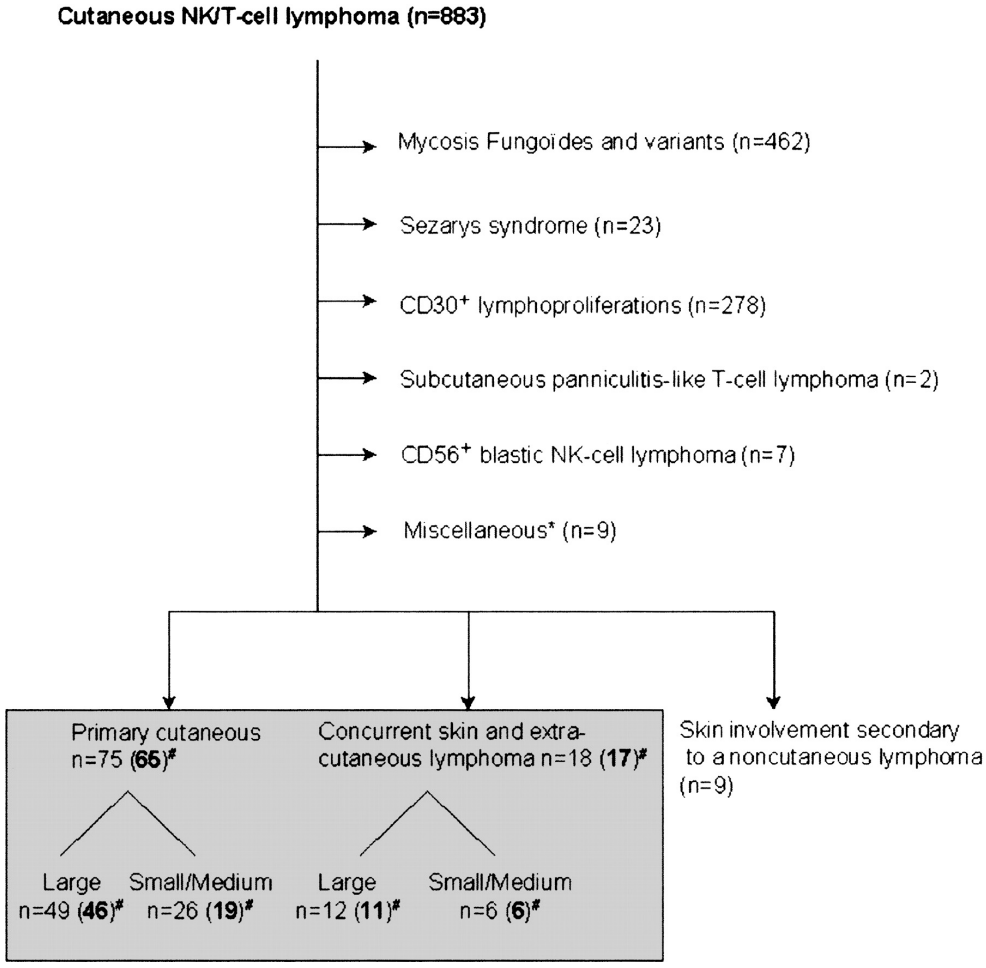

Figure 1. Patients with cutaneous T/NK-cell lymphomas included in the registry of the Dutch Cutaneous Lymphoma Group between October 1985 and December 2000. *"Miscellaneous" includes patients with T-cell leukemia (n - 4), HIVrelated CTCL (n - 2), adult T-cell lymphoma/ leukemia (n - 2), and T-lymphoblastic lymphoma (n - 1). #Numbers in parentheses denote number of patients included in this study.

In all cases the clinical records and the results of routine histology and immunostaining performed at diagnosis were reviewed. In cases in which the original paraffin blocks were available, additional staining was performed using antibodies against CD3, CD4, CD8, CD20, CD79a, CD30, CD56, CD68, TIA-1, and granzyme B, if not performed previously.

Biopsy samples of all cases were re-evaluated at a multiheaded microscope by 3 expert (dermato)pathologists (C.J.L.M.M., P.M.K., R.W.) and a consensus diagnosis was reached.

From the initial study group of 93 cases, 11 cases were excluded: 2 patients because of insufficient follow-up data, 3 patients with unavailable or uninterpretable histology, and 6 patients in whom after thorough clinical and histologic review a diagnosis of MF was considered more likely. The final study group consisted of 82 cases.

In all cases the diagnosis of T-cell lymphoma was based on demonstration of mature, although often incomplete, T-cell phenotype, including expression of surface CD3 (sCD3) as assessed by a positive membrane staining with monoclonal antibody Leu-4 on frozen sections in all but 7 cases. Staining for CD30 antigen was completely negative in most cases, expressed by few (< 5%) scattered neoplastic cells in some cases, and weakly expressed by approximately 25% of the neoplastic T-cells in one case.

Statistical analysis

Variables analyzed for prognostic value were as follows: age at diagnosis; sex; extent of skin lesions at presentation (ie, single or localized [a solitary or multiple skin lesions restricted to one anatomic region] vs "multifocal" [2 or more anatomic regions involved]); the presence of extracutaneous disease at the time of diagnosis; occurrence of spontaneous resolution; type of therapy (multiagent chemotherapy vs radiotherapy vs monoagent chemotherapy vs no or only palliative skin-directed therapies such as psoralen and ultraviolet A [PUVA], topical steroids, and excision); tumor cell size (more vs less than 30% large neoplastic T-cells); and phenotype (CD3+CD4+CD8– phenotype vs CD3+CD4–CD8+ phenotype vs CD3+CD4–CD8– phenotype vs CD3+CD4+CD8+ phenotype). Disease-free survival (DFS) was calculated as the time of relapse or disease-related death after reaching a complete remission. Cases that did not reach remission were excluded; patients without a relapse or death unrelated to lymphoma were censored. Survival duration was calculated from time of diagnosis to date of death or censoring. Overall survival was estimated using the method of Kaplan and Meier.[7] For overall survival analysis, deaths were taken into account whatever the cause. Prognostic factors in the entire group were evaluated by overall survival univariate and multivariate analyses using a Cox proportional hazards model. Factors significant at the .1 level in univariate analysis were included in a stepwise regression multivariate analysis. Comparisons between different subgroups of patients were performed using the 2 of Fisher exact test for categorical variables (cross-table) or the Mann-Whitney test for continuous variables and log rank for survival data. For statistical analysis the software package for social sciences (SPSS 10.0; SPSS, Chicago, IL) was used.

Results

Characteristics of the total group of 82 patients with PTL, unspecified

Clinical features

The clinical characteristics and follow-up data of the total group of 82 patients are summarized in **Table 1**. The total group included 50 males and 32 females (male-female ratio, 1.6:1), with a median age of 68 years (range, 8-87 years). The duration of skin lesions prior to diagnosis varied between 1 and 100 months, but was usually short (median, 6 months). Most patients

presented with nodular or tumorous skin lesions, which were either solitary (21 of 82 [26%]), localized (11 of 82 [13%]), or multifocal (50 of 82 [61%]). Partial (n = 10) or even complete (n = 3) spontaneous disappearance of skin lesions had been noted in 13 of the 82 patients.

Initial therapy was variable, but consisted in most cases of doxorubicin-based systemic chemotherapy, radiotherapy, or a combination of both. In general, radiotherapy was the first choice of treatment in patients presenting with only localized skin lesions, whereas patients presenting with multifocal skin lesions or with concurrent cutaneous and extracutaneous disease were treated with doxorubicin-based chemotherapy with or without additional radiotherapy. Complete remission was achieved in 22 (71%) of 31 patients treated with radiotherapy and in 10 (28%) of 36 patients treated with doxorubicin-based chemotherapy. However, complete remissions were generally short-lived. The median DFS for complete responders was only 8 months (95% confidence interval [CI], 2-14 months). No correlation between initial type of treatment and clinical outcome was detected.

After a median follow-up of 19 months (range, 1-179 months) 60 patients (73%) had died of lymphoma and 9 (11%) had died of unrelated disease, whereas only 13 patients were alive, with (n = 1) or without (n = 12) lymphoma. The overall 5-year survival was 20% (**Table 1**).

Histologic features

Histologically, these lymphomas showed considerable variation. On the basis of the cytomorphology of the neoplastic cells, most cases would have been classified as pleomorphic T-cell lymphoma in the updated Kiel classification.[8] A minority showed a monotonous proliferation of blasT-cells with the appearance of immunoblasts, in 2 cases even resembling large anaplastic T-cells, but with negative CD30 staining in repetitive stainings. Based on the presence of more or less than 30% large cells within the tumor population, 57 cases were classified as large-cell and 25 cases as small- or medium-sized-cell lymphoma. There was a variable admixture with small lymphocytes and histiocytes, and less commonly with eosinophils and plasma cells. Considerable numbers of admixed B-cells (5%-10%) were observed in 6 biopsies.

With respect to the architecture of the neoplastic infiltrates, these were either diffuse (49%), nodular (33%), or band-like (18%). Pronounced epidermotropism was observed in 27% of cases, with no significant differences between the different subgroups. In 3 cases there was extensive infiltration of the follicular epithelium. Angiocentricity with marked angiodestruction was observed in 8 cases; 5 of these 8 cases belonged to the group of primary cutaneous small/medium-sized pleomorphic T-cell lymphomas.

Table 1. Cumulative results for the total group and 3 subgroups of primary and secondary CD30⁻ peripheral T/NK-cell lymphomas

	Total	Primary CTCL, large cell	Primary CTCL, small/medium cell	Concurrent CTCL*
Patients, no.	82	46	19	17
Sex ratio, male-female	50:32	33:13	6:13	11:6
Age, median, y (range)	68 (8-87)	68 (20-87)	69 (45-87)	65 (8-85)
Extent of skin lesions, no.				
Solitary	21	15	4	2
Localized	11	4	5	2
Multifocal	50	27	10	13
Spontaneous remission, no.				
Absent	69	39	13	16
Partial	10	6	4	1
Complete	3	1	2	0
Initial therapy, no.				
Radiotherapy	31	19	12	0
Multiagent chemotherapy	36†	18‡	5	13§
Excision	2	2	0	0
PUVA	3	1	0	2
Monochemotherapy	6§	3	1§	2
None	4	3	1	0
Result of initial therapy, no.				
Complete remission	36	21	12	3
Partial remission	27	13	6	8
No response/progression	19	12	1	6
Relapse, no.				
Skin only	15	9	6	0
Systemic	58	34	7	17
None	9	3	6	0
Follow-up, median, mo (range)	19 (1-179)	21 (1-118)	47 (9-143)	8 (1-179)
Current status, no.				
No evidence of disease	12	4	7	1
Alive with disease	1	0	1	0
Died of lymphoma	60	37	8	15
Died of other cause	9	5	3	1
Phenotype, no.				
$CD4^-/CD8^-$	59	34	13	12
$CD4^-/CD8^+$	12	6	4	2
$CD4^-/CD8^-$	9	5	2	2
$CD4^-/CD8^+$	2	1	0	1
Overall survival, %				
5 y	20	12	45	12
10 y	8	NR	19	NR
Median survival, mo	21	22	56	8

Numbers are absolute number of patients uless indicated otherwise.
NR indicates not reached.
*Both skin and extracutaneous disease at time of diagnosis.
†Six of these patients received additional radiotherapy.
‡Five of these patients received additional radiotherapy.
§One of these patients received additional radiotherapy.

Immunophenotype

The phenotypes of the neoplastic T-cells in all 82 cases are summarized in TABLE 2. A CD3+/CD4+/CD8– phenotype was observed in 59 cases, a CD3+/CD4–/CD8+ phenotype in 12 cases, a CD3+/CD4–/CD8– phenotype in 9 cases, and a CD3+/CD4+/CD8+ phenotype in 2 cases. Coexpression of CD56 was noted in 3 cases. Expression of TIA-1 by more than 50% of the neoplastic cells was observed in 17 of 55 cases tested, including 5 (13%) of 38 cases with a CD3+/CD4+/CD8– phenotype and 8 (89%) of 9 cases with a CD3+/CD4–/CD8+ phenotype. Granzyme B was always expressed by a minor proportion of the TIA-1+ neoplastic T-cells, except for 2 cases with a CD3+/CD4–/CD8+ and a CD3+/CD4–/CD8–

Table 2. Immunophenotype of 82 peripheral T-cell lymphomas presenting in the skin

Lymphoma	Phenotype				Total
	$CD3^+CD4^+CD8^-$	$CD3^+CD4^-CD8^+$	$CD3^+CD4^-CD8^-$	$CD3^+CD4^+CD8^+$	
Primary cutaneous, large cell	34	6	5	1	46
Primary cutaneous, small/medium-sized cell	13	4	2	0	19
Concurrent cutaneous and extracutaneous disease	12	2	2	1	17
Total no. of patients	59	12	9	2	82

phenotype, respectively, showing expression of both TIA-1 and granzyme B by more than 75% of the neoplastic T-cells.

Prognostic factors in the total group of 82 patients

Univariate and multivariate analyses of overall survival were performed on the total group of 82 patients to identify independent prognostic risk factors. Univariate analysis showed that the following variables were adversely related to survival: concurrent extracutaneous disease at diagnosis (P = .0004), large cell size (P = .003), lack of spontaneous resolution (P = .004), age older than 70 years at diagnosis (P = .02), male sex (P = .05), and presentation with multifocal lesions (P = .005). Therapy (P = .19) was not significantly related to survival. Multivariate analysis showed that concurrent extracutaneous disease (relative risk [RR] = 3.5; 95%CI,1.9-6.8), large cell morphology (RR = 3.1; 95%CI, 1.7-5.7), presentation with multifocal lesions (RR = 2.3; 95%CI, 1.4-4.0), age older than 70 years (RR = 2.1; 95%CI, 1.3-3.6), and absence of spontaneous resolution of skin lesions (RR = 2.6; 95%CI, 1.1-5.9) were independent prognostic factors (**TABLE 3**). Kaplan-Meier overall survival and DFS curves of different subgroups are shown in **FIGURE 2A** and **2B**, respectively.

Table 3. Results from overall survival multivariate analysis of 82 patients with a peripheral T-cell lymphoma presenting in the skin

	RR (95% CI)	*P*
Extracutaneous localization at diagnosis		<.0001
No*	1	
Yes†	3.5 (1.8-6.8)	
Cell size		<.0001
Small/medium	1	
Large	3.1 (1.7-5.7)	
Extent		.002
Solitary/localized	1	
Multifocal	2.3 (1.4-4.0)	
Age, y		.004
Younger than 70	1	
70 or older	2.1 (1.3-3.6)	
Spontaneous resolution		.02
Yes	1	
No	2.6 (1.1-5.9)	

RR indicates relative risk; CI, confidence interval.
*Primary CTCL.
†Concurrent CTCL.

Subgroup analysis

Since multivariate analysis demonstrated both cell size and the presence of extracutaneous disease at the time of diagnosis as the most significant prognostic parameters, the main features of the group of primary cutaneous CD30– large T-cell lymphomas, the group of

primary cutaneous small/medium-sized pleomorphic T-cell lymphomas, and the group of peripheral T-cell lymphomas presenting with both cutaneous and extracutaneous disease will be described below. The main clinical features and the results of phenotyping of these 3 groups are summarized in **TABLES 1** and **2**, respectively.

Primary cutaneous CD30– large T-cell lymphomas (n = 46)

This group included 33 males and 13 females (male-female ratio, 2.5:1), with a median age of 68 years (range, 20-87 years). Although most patients presented with multifocal skin lesions (27 of 46 patients [59%]), a significant proportion had either a solitary lesion (15 of 46 patients

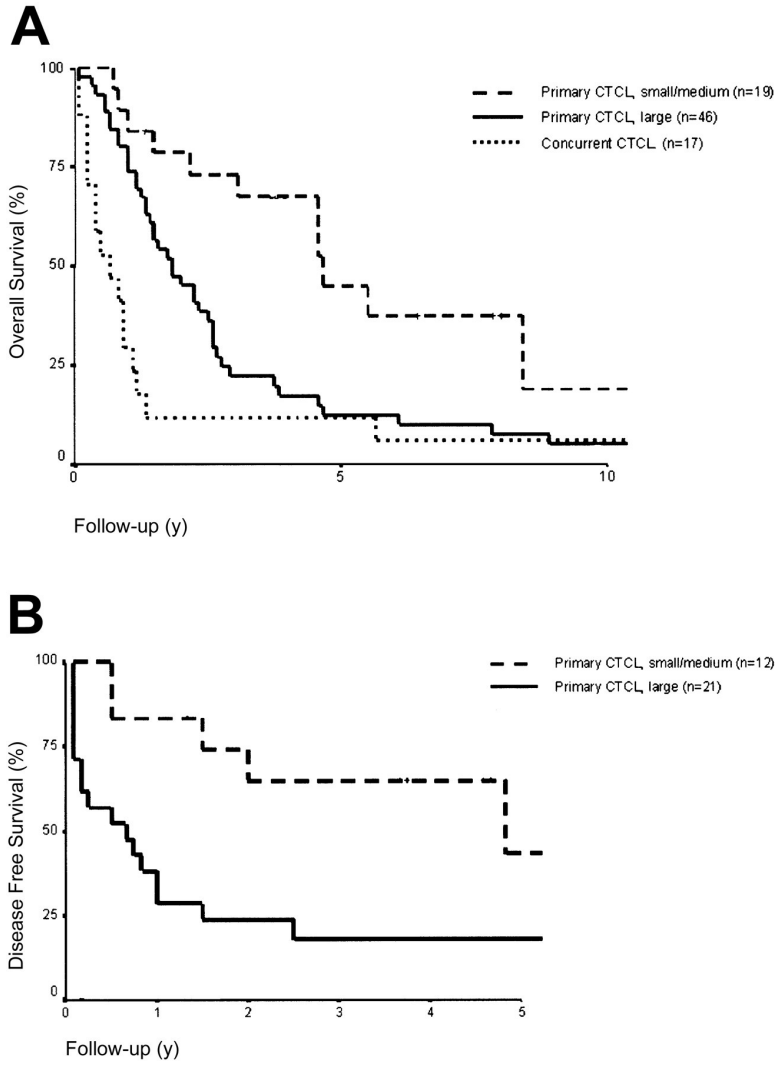

FIGURE 2. Overall and disease-free survival curves. (A) Overall survival curves of different groups of patients with peripheral T-cell lymphomas presenting in the skin (n

[33%]) or localized skin lesions (4 of 46 patients [9%]) at presentation, which explains the relatively high number of patients treated with radiotherapy in this group (**Table 1**).

Following initial treatment, complete remission was achieved in only 21 (45%) of 46 patients, including 12 (63%) of 19 patients treated with radiotherapy and 5 (27%) of 18 patients treated with doxorubicin-based chemotherapy. The median overall survival for patients treated with radiotherapy was 28 months (95% CI, 12-44 months); the DFS for this group was 6 months (95% CI, 0-18 months). For patients treated with systemic chemotherapy, the median overall survival was 16 months (95% CI, 10-22) and DFS was 10 months (95% CI, 0-25 months). With respect to the extent of skin disease, complete remission following initial treatment was observed in 21 of 46 patients, including 13 (86%) of 15 patients with a solitary lesion, but only 1 (25%) of 4 patients with localized lesions and 7 (26%) of 27 patients presenting with multifocal lesions.

However, no difference in overall survival was found between patients with localized disease (median, 24 months; 95% CI, 13-35 months) and patients with multifocal disease (median, 21 months; 95% CI, 13-29 months). In patients presenting with a solitary tumor, radiotherapy (11 cases) and doxorubicin-based chemotherapy (4 cases) showed similar complete response rates (72% vs 75%), median DFS rates (6 months, 95% CI, 10-28 months vs 10 months, 95% CI, 10-24 months), and overall 5-year-survival rates (24% vs 25%). These data illustrate that most patients presenting with solitary or localized skin lesions rapidly developed generalized skin lesions and/or systemic disease. After a median follow-up of 21 months (range, 1-118 months), 42 patients had died (37 patients of lymphoma and 5 of an unrelated disease), whereas only 4 were still alive and in complete remission, 20, 31, 89, and 118 months after diagnosis. One of these 4 patients presented with a solitary nodule on the right shoulder, histologically characterized by the presence of a monotonous proliferation of CD3+CD4+CD8– blasT-cells with prominent eosinophilic nucleoli, suggesting a CD30+ anaplastic large T-cell lymphoma, but with negative CD30 stainings on 3 different (follow-up) biopsies. Another patient presented with a solitary tumor on the trunk, in which approximately 25% of the CD3+CD4+ large pleomorphic T-cells expressed CD30. Both patients had initially been treated with radiotherapy. The other 2 patients had presented with multifocal skin lesions, which had disappeared spontaneously in one of them. Five-year overall survival in this group of 46 patients was 12%.

Statistical analysis showed no significant difference (P = .98) in overall survival between the 34 patients with a CD3+CD4+CD8– phenotype (median survival, 21 months; 95% CI, 11-31 months) and the 6 patients with a CD3+CD4–CD8+ phenotype (median survival, 28 months; 95% CI, 14-42 months; **Table 4**).

Primary cutaneous small/medium-sized cell CD30– pleomorphic T-cell lymphoma

This group included 6 men and 13 women, with a median age of 69 years (range, 45-87 years). Ten patients presented with multifocal skin lesions, 5 with localized disease, and only 4 with a solitary lesion. In a relatively large proportion of patients (32%), partial (4 cases) or even complete (2 cases) spontaneous clearing of the skin lesions was noted.

Histologically, 5 of 19 patients showed marked angiocentricity and angiodestruction. Previous studies on this group, including 3 cases with a CD4+ phenotype and 2 cases with a CD8+ phenotype, had shown that they were Epstein-Barr virus (EBV)–negative.[9] In the whole group, 13 cases (68%) had a CD3+CD4+CD8– phenotype; 4 cases (21%), a CD3+CD4–CD8+ phenotype; and 2 cases (10%), a CD3+CD4–CD8– phenotype (TABLE 2).

Table 4. Calculated median overall survival (Kaplan-Meier) of subgroups of patients with peripheral T-cell lymphomas presenting in the skin

	Phenotype									
	$CD3^+CD4^+CD8^-$		$CD3^+CD4^-CD8^+$		$CD3^+CD4^-CD8^-$		$CD3^+CD4^+CD8^+$		Total	
	OS, mo (95% CI)	No.	OS, mo (95% CI)	No.	OS, mo (95% CI)	No.	OS, mo (95% CI)	No.	OS, mo (95% CI)	No.
Primary cutaneous, all	27 (15-39)	47	28 (9-47)	10	19 (11-27)	7	NR	1	28 (20-36)	65
Primary cutaneous, large cell	21 (11-31)	34	28 (14-42)	6	19 (13-25)	5	NR	1	22 (14-30)	46
Primary cutaneous, small/medium-sized cell	56 (16-96)	13	12 (0-57)	4	10 (NR)	2	—	0	56 (35-77)	19
Concurrent cutaneous and extracutaneous disease	10 (5-15)	12	3 (NR)	2	1 (NR)	2	NR	1	8 (1-15)	17
Total group of patients	24 (15-33)	59	18 (0-45)	12	16 (0-34)	9	1 (NR)	2	21 (12-30)	82

OS indicates overall survival; CI, confidence interval; NR, not relevant.

Following initial treatment, 12 (63%) of 19 patients reached a complete remission, including 10 (83%) of 12 treated with radiotherapy and 2 (40%) of 5 patients treated with doxorubicinbased chemotherapy. The median DFS for the complete responders was 58 months (95% CI, 0-120 months). After a median follow-up of 47 months (range, 9-120 months), 8 patients had died of lymphoma, 3 had died of unrelated disease, and 8 were alive with (n = 1) or without (n =7) lymphoma. Overall 5-year survival was 45%. Univariate and multivariate analysis for overall survival showed that patients presenting with localized disease had a better prognosis (P = .03). Overall median survival was significantly better in patients with localized disease (median survival not reached) than in patients presenting with multifocal skin lesions (median survival, 54 months; 95% CI, 22-88 months). Patients with a CD4+ phenotype tended to have a better prognosis, but this was only borderline statistically significant (P = .05). Owing to the small number of patients, the significance of these findings should be considered with caution. Nevertheless, 6 of the 7 patients presenting with solitary or localized skin lesions and having a CD3+/CD4+ phenotype are alive at the time of writing, as compared with 2 of 12 of the remaining cases in this group.

Taken together, patients with a primary cutaneous CD30– small/medium-sized pleomorphic T-cell lymphoma had a much better prognosis than did patients with a primary cutaneous CD30– large T-cell lymphoma. However, this favorable prognosis appears to be restricted to patients with a CD4+ lymphoma with solitary or localized skin lesions.

PTL, unspecified, presenting with both cutaneous and extracutaneous disease

This group contained 6 cases with a predominance of small/medium-sized neoplastic T-cells and 11 cases with a predominance of large neoplastic T-cells. Statistical analysis did not reveal significant differences between the 2 groups (data not shown). The results for the total group of 17 patients (11 males and 6 females, with a median age of 65 years [range, 8-85 years]) are presented in Table 1. Most (13) of the 17 patients presented with multifocal skin lesions. Concurrent extracutaneous disease at presentation involved lymph nodes (14 cases), bone marrow (2 cases), peripheral blood (2 cases), oropharynx (2 cases), central nervous system (CNS; 1 case), and lung and adrenal glands (1 case).

Initial treatment, which consisted of multiagent chemotherapy in 13 of 17 patients, resulted in a complete remission in only 3 of 17 cases; 8 patients showed a partial response. The prognosis is clearly worse in this group than in the primary cutaneous CD30– groups ($P < .0001$). After a median follow-up period of 8 months (range, 1-179 months), 15 patients had died of lymphoma and one of unrelated disease, whereas only one patient was still alive after a follow-up of 179 months. The overall 5-year survival was 12%.

Discussion

In the present study, 82 patients with a PTL, unspecified, with skin lesions as first manifestation of the disease were evaluated. The goal of this study was to find independent parameters of survival in this heterogeneous group of lymphomas. More specifically, we wondered if presentation with only skin lesions, the extent of skin lesions, cell size, or the presence of a CD4+ or CD8+ T-cell phenotype had any effect on survival.

Considering the whole group, these patients appeared to have a poor prognosis, with an overall survival at 5 years of 20%, which is consistent with the results of previous studies.[10-12] It was found that primary cutaneous -small/medium-sized T-cell lymphomas had a much better prognosis than primary cutaneous CD30– large T-cell lymphomas and patients presenting with both cutaneous and extracutaneous disease. The difference in survival between primary cutaneous large-cell and small/medium-sized-cell lymphomas is consistent with the results of previous studies.[4,5] A new finding in the present study was that this favorable prognosis was observed only in cases with a CD3+CD4+CD8– phenotype and presenting with solitary or

localized skin lesions. Five of 6 patients in this small subgroup were still alive, compared with 8 of 76 patients who did not belong to this group.

Primary cutaneous CD30– small/medium-sized pleomorphic T-cell lymphoma is a diagnosis by exclusion. Confronted with a CTCL with a neoplastic infiltrate showing a predominance of small- to medium-sized pleomorphic T-cells, the clinician should exclude diagnoses of tumor stage MF, SS, lymphomatoid papulosis, subcutaneous panniculitis-like T-cell lymphoma, and pseudo–T-cell lymphoma. Particularly, differentiation from (tumor stage) MF and pseudo–T-cell lymphomas may be difficult, and requires detailed analysis of clinical, histologic, and immunophenotypic data.[13-15] In this study, 4 cases originally diagnosed as small/medium-sized pleomorphic CTCL were excluded, since in retrospect a diagnosis of MF was considered more likely. Pseudo–T-cell lymphomas characteristically present with a solitary plaque or nodule. Additional criteria favoring a pseudo–T-cell lymphoma include lack of an aberrant T-cell phenotype, lack of clonality, and a considerable admixture with reactive CD8+ T-cells, B-cells, and histiocytes.[13,14] In a recent EORTC workshop on primary cutaneous small/medium-sized pleomorphic T-cell lymphomas, the large majority of submitted cases concerned patients presenting with a solitary lesion, which also proved to have an excellent prognosis (J. Wechsler, manuscript in preparation).

After exclusion of the small subgroup of CD3+CD4+CD8– small/medium-sized pleomorphic CTCLs with solitary or localized skin lesions, neither presentation with skin-limited disease, cell size, extent of skin lesions at presentation, nor phenotype had any significant effect on survival. All subgroups had a poor prognosis, with a median overall survival of 28 months or less (**Table 4**).

From a clinical point of view it is important to note that, apart from the group of primary cutaneous small/medium-sized CD4+ T-cell lymphomas, patients presenting with a solitary skin lesion or a few localized skin lesions had no better survival than patients presenting with multifocal skin lesions. In the group of primary cutaneous CD30– large T-cell lymphomas, which comprised 46 of 82 patients, the median overall survival for patients presenting with solitary, localized, or multifocal skin lesions was 24, 12, and 21 months, respectively. These observations illustrate that patients presenting with solitary or localized skin lesions almost without exception rapidly develop widespread disease.

The results of the present study also indicate that current treatment strategies in these PTLs, unspecified, are not effective, which is in agreement with the results of previous studies.[10-12] Comparison of the type of treatment between survivors and nonsurvivors did not show major differences. In the group of 13 survivors, which included 9 patients presenting with only

solitary or localized skin lesions, 8 patients had been treated with radiotherapy and only 3 with doxorubicin-based chemotherapy. Following the guidelines of the Dutch Cutaneous Lymphoma Group, most patients with only solitary or localized skin lesions at presentation were treated with radiotherapy, whereas patients presenting with multifocal skin lesions or with concurrent cutaneous and extracutaneous disease were generally treated with doxorubicin-based chemotherapy (CHOP [cyclophosphamide, doxorubicin, vincristine, and prednisone] or CHOP-like courses), with additional radiotherapy in some cases. Initial radiotherapy resulted in a complete remission in 22 (71%) of 31 patients. However, these complete remissions were generally short-lived, requiring additional multiagent chemotherapy soon afterward. In general, a beneficial effect of radiotherapy may be expected only in the subgroup of primary cutaneous CD3+/CD4+ small/medium-sized pleomorphic CTCLs presenting with solitary or localized skin lesions. The results of doxorubicin-based chemotherapy were equally disappointing, both in patients presenting with solitary or localized disease and in patients presenting with multifocal skin lesions or with concurrent extracutaneous disease. Complete remission was observed in only 10 (28%) of 36 patients, and the median DFS for complete responders was only 3 months (95% CI, 0-15 months). Recent studies suggest that more intensive regimens are also not effective in these PTLs, unspecified.[10,11] Two patients in the present study were treated with intensive chemotherapy followed by autologous bone marrow transplantation, but they also experienced relapses and died of lymphoma (12 and 49 months after transplantation). It is fair to conclude that it is as yet unknown how such patients with a PTL, unspecified, can best be treated. Because of the inefficacy of current standard regimens, new therapies should be investigated in prospective trials.

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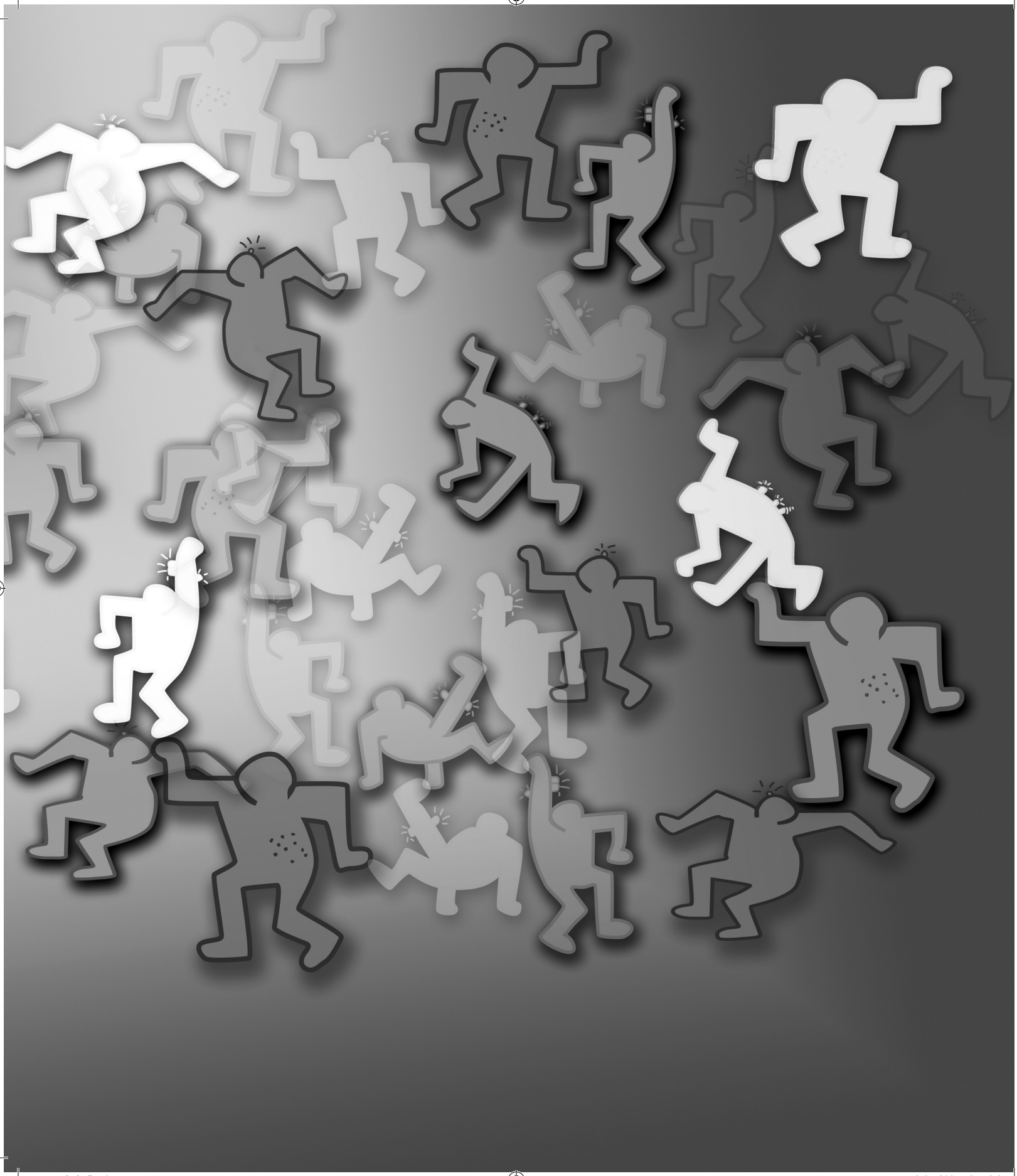

chapter 4

CD56+ hematological neoplasms presenting in the skin: a retrospective analysis of 23 new cases and 130 cases from the literature

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Marcel W Bekkenk [1]
Patty M Jansen [2]
Chris JLM Meijer [3]
Rein Willemze [1]

1. Department of Dermatology, Leiden University Medical Center, The Netherlands
2. Department of Pathology, Leiden University Medical Center, The Netherlands
3. Department of Pathology, the Vrije Universiteit Medical Center, Amsterdam, The Netherlands

ABSTRACT

Background

To define prognostic parameters and guidelines for diagnosis and treatment for CD56+ lymphomas and leukemias with first presentation in the skin.

Patients and Methods

The studygroup included 153 cases (23 new and 130 from literature). According to the WHO classification the group included 15 nasal and 38 nasal-type NK/T-cell lymphomas, 63 blastic NK-cell lymphomas, 14 cutaneous CD30+ lymphoproliferations, 10 cases of myeloid leukemia, 6 cases of subcutaneous panniculitis-like T-cell lymphoma and 7 peripheral T-cell lymphomas, unspecified.

Results

In general these CD56+ lymphomas/leukemias had a poor prognosis with only 27% of patients alive after a median follow-up of 12 months. The median survival was 13 months. Nasal and nasal-type NK/T-cell lymphomas and CD56+ SCPLTCL, had the worst prognosis with a median survival of 5, 6 and 5 months, respectively. Only nasal-type NK/T-cell lymphomas presenting with only skin lesions had a somewhat better prognosis (median survival, 27 months). In blastic NK-cell lymphomas (median survival, 14 months), age ≤ 40 years, aggressive treatment with acute leukemia protocols and high TdT expression were associated with a more favorable prognosis. Striking similarities in histology, immunophenotype, clinical presentation and clinical behavior were found between blastic NK-cell lymphomas and CD56+ myeloid leukemias.

Conclusion

CD56+ lymphomas/leukemias presenting in the skin have a poor prognosis except for primary cutaneous CD30+ lymphoproliferations. The striking similarities between blastic NK-cell lymphomas and CD56+ myeloid leukemias presenting in the skin provide a rationale to treat these patients with more aggressive regimens used in myeloid leukemias rather than with CHOP(-like) regimens.

INTRODUCTION

The availability of monoclonal antibodies against CD56 that are active in paraffin sections has resulted in the recognition of a subgroup of cutaneous lymphomas derived from natural killer (NK) cells or NK-like T-cells. CD56 or neuronal-cell adhesion molecule (N-CAM) is a 175 to 185 kd surface glycoprotein involved in cell adhesion and migration, which is expressed on all NK-cells and subsets of CD4+ and CD8+ T-cells and monocytes.[1]

These CD56+ T/NK-cell lymphomas preferentially present at extranodal sites, not

uncommonly the skin, and almost without exception have an extremely poor prognosis. In the WHO classification several groups of CD56+ lymphomas are distinguished, including extranodal NK/T-cell lymphoma, nasal/nasal-type and blastic NK-cell lymphoma.[2] Nasal NK/T-cell lymphoma, previously designated lethal midline granuloma, typically presents in the nasopharynx and often shows an angiocentric growth pattern with prominent necrosis and vascular destruction. The neoplastic cells express cytotoxic proteins (TIA-1, granzyme B and perforin) in most cases. These lymphomas have been reported most frequently in Asia and Central and South America, and are almost without exception strongly associated with Epstein Barr virus (EBV). Lymphomas with similar histology and phenotype arising at other extranodal sites are designated extranodal NK/T-cell lymphoma, nasal-type.

Blastic NK-cell lymphoma most commonly presents in the skin with or without concurrent extracutaneous disease. Histologically, these lymphomas are characterized by a diffuse monotonous infiltrate of medium-sized cells resembling lymphoblasts or myeloblasts. Characteristically, the neoplastic cells are positive for CD4 and CD56 and in some cases for TdT, but do not express surface CD3 and cytotoxic proteins, and are not associated with EBV.

In addition to these three groups, cases of myeloid leukemia presenting primarily in the skin as well as other well-defined types of CTCL, such as primary cutaneous CD30+ (anaplastic) large T-cell lymphomas, subcutaneous panniculitis-like T-cell lymphoma (SCPLTCL) and CD8+ epidermotropic CTCL, may show co-expression of CD56 in a proportion of cases.

These CD56+ (cutaneous) lymphomas are an extremely difficult group both for pathologists and clinicians. For pathologists correct classification of these lymphomas is difficult, expensive and time-consuming, since it requires application of several complimentary techniques, such as extensive phenotyping, EBV analysis and T-cell receptor (TCR) gene rearrangement studies. It is therefore important to know if such a detailed analysis is useful from a therapeutic or prognostic point of view. Clinicians are confronted with an aggressive clinical behavior and a fatal outcome often within a year after diagnosis, and may consider more intensive therapies as in acute leukemia's as initial therapy. Whether patients presenting with only localized skin lesions have a somewhat better prognosis, and require another therapeutic approach is uncertain. It is also unknown whether co-expression of CD56 in well-defined types of CTCL is associated with a more unfavorable prognosis, and should be treated more aggressively.

In an attempt to answer some of these questions and to better define these different subgroups we evaluated the clinicopathologic and immunophenotypical data of a large group of CD56+ lymphomas/leukemias presenting in the skin, including 23 new cases and 130 cases from literature.

MATERIAL AND METHODS

Patients

The two main selection criteria for this study were CD56 expression by the neoplastic T/NK-cells or myeloid-cells and the presence of skin lesions at the time of first diagnosis. Twenty-three patients meeting both criteria were found in the registry of the Dutch Cutaneous Lymphoma Group. Fourteen patients had been diagnosed in the last two years, when CD56 staining had been routinely applied. Retrospective analysis of a large group of CTCL other than mycosis fungoides and cases of leukemia cutis (presenting with skin lesions) yielded another nine CD56+ cases. Sixteen of 23 patients had only skin lesions at the time of diagnosis as assessed with routine staging procedures,[3] whereas 7 patients had presented with concurrent cutaneous and extracutaneous disease. Additional immunostainings for CD2, CD3, CD4, CD5, CD7, CD8, CD30, CD68, TIA-1, granzyme B and myeloperoxidase and in situ hybridization for EBER were performed, when appropriate and possible. The clinical and histological data were retrieved and re-evaluated, and all cases were classified according to the criteria of the WHO-classification.[2]

REVIEW OF LITERATURE

Our literature search focused on reports of CD56+ lymphomas/leukemias with

a) skin lesions at presentation,
b) a follow-up of at least 12 months unless prior death to lymphoma, and
c) sufficient immunophenotypical data to allow categorization according to the WHO-classification.[2]

A Medline survey using "skin" and "CD56" in the PubMed search engine including papers until 1st of December 2002, revealed 87 English papers containing patients with a cutaneous CD56-positive lymphoma/leukemia. Fifty-seven papers included CD56+ lymphomas/leukemias with skin lesions at first presentation, which had been designated variously as nasal(-type) NK/T-cell lymphoma, NK/T-cell lymphoma, angiocentric lymphoma, blastic NK-cell lymphoma, lymphoblastic NK-cell lymphoma, NK-cell leukemia/lymphoma, CD4+/CD56+ ("hematodermic") lymphoma, CD30+/CD56+ lymphoma, myeloid leukemia, granulocytic sarcoma, cytotoxic T-cell lymphoma, SCPLTCL, lymphomatoid papulosis and (primary cutaneous) CD30+ (anaplastic) lymphoma[4-60].

A total number of 130 cases met all three criteria mentioned above. Using the WHO-classification[2] these cases from literature included 14 nasal NK/T-cell lymphomas, 38 extranodal NK/T-cell lymphomas, nasal-type, 52 blastic NK-cell lymphomas, 10 cutaneous CD30+ lymphoproliferations, 7 cases of AML, 5 cases of SCPLTCL, and 4 peripheral T-cell lymphoma, unspecied (all with co-expression of CD56).

Statistical analysis

Comparison between different subgroups of patients were performed using the chi-square of Fisher's exact test for categorical variables (cross-table) or Mann-Whitney test for continuous variables. Survival duration was calculated from time of diagnosis to date of death or censoring. Overall survival rates were estimated using the method of Kaplan and Meier[61]. For overall survival analysis deaths were taken into account whatever the cause, disease specific analysis was not performed because only one case died from an unrelated cause.

Prognostic factors in the different subgroups were evaluated by overall survival univariate and multivariate analyses using a Cox proportional hazards model. Factors significant at the 0.1 level in univariate analysis were included in a stepwise regression multivariate analysis.

The following parameters were analyzed: clinical prognostic factors including gender, age, extent of cutaneous and extracutaneous disease and therapy; histological factors including cell-size, angiocentricity, expression of cytotoxic proteins and expression of several immunohistochemical markers, in particular CD30 and TdT, expression of EBV and the presence of clonal T-cell rearrangement, if performed or described.

For statistical analysis the software package for social sciences (SPSS 10.0, Chicago Illinois) was used.

Results

The clinical, histological and immunophenotypical data of our 23 new cases are summarized in tables **1** and **2**. Cumulative data on the whole group of 153 cases are summarized in tables **3** and **4**, and described below.

Total group (n=153)

The total group consisted of 89 male and 56 female patients (male:female ratio= 1,6:1), whereas no information on gender was available in 8 cases. The median age was 56 years (range 2-94 years). Sixty-seven of 153 (44%) cases had no evidence of extracutaneous disease at presentation. Treatment mostly consisted of multiagent chemotherapy (69%). A complete remission was reached in 47% of the cases, but 89% relapsed usually after only a short time. The prognosis was poor with a median survival of 12 months (95% CI: 9-15 months), a 2-year-survival of 34% and a 5-year-survival of 12%. (see table **4**) The two largest groups were the blastic NK-cell lymphomas (n=63) and the nasal (n=15) and nasal-type (n=38) NK/T-cell lymphomas (n=53).

Nasal NK/T-cell lymphoma (n=15)

This group consisted of 10 males and 5 females with a median age of 58 years (range 19-90 years). All cases presented with lesions in the nasopharyngeal area combined with skin lesions, whereas other sites were affected infrequently (see table **4**). Initial treatment, mostly

multiagent chemotherapy (73%), resulted in a complete remission in only 3 cases. All cases died of lymphoma. This was the group with the worst prognosis; the median survival was only 5 months, whereas the 2-year-survival was not reached (see TABLE **4**). Two cases were of T-cell origin as proven by TCR and CD3s expression.

Nasal-type NK/T-cell lymphoma (n=38)

This group included 19 males, 15 females and 4 cases with unknown gender. The median age at diagnosis was 50 years (range 16-79 years). Fifteen of 38 cases presented with only skin

Table 1. Clinical data of 23 new patients

Case	Diagnosis	Sex/age (years)	Presentation	Treatment	Result	Sites at relapse	Status	Follow-up (months)
1	Nasal NK/T	M/90	Tumor on the nose and in paranasal sinus	RT	CR	Skin	D+	6
2	Nasal-type NK/T	F/49	Ulcus right leg, generalized papules and involved right inguinal lymph node	Prednisone	Progression	Hemocytophagic syndrome	D+	3
3	Nasal-type NK/T	M/66	Solitary ulcerative tumor on right elbow	None	CR	None	Ao	22
4	Blastic NK	F/15	Generalized tumors	CHOP	NR	Skin	A+	24
5	Blastic NK	F/41	Localized tumors	Unknown	Unknown	Skin	A+	12
6	Blastic NK	F/87	Localized plaques on leg	RT	CR	CNS, skin	D+	6
7	Blastic NK	M/71	Localized plaques in the face and BM involvement	RT	PR	Skin, BM	D+	20
8	Blastic NK	M/77	Generalized tumors and peripheral lymph node involvement	CHOP+RT	Progression	CNS, skin	D+	12
9	Blastic NK	M/76	Generalized tumors and BM involvement	CHOP	CR	Skin	D+	10
10	Blastic NK	M/67	Generalized tumors and involved left axillairy lymph node	CHOP	CR	Skin	D+	12
11	Blastic NK	M/76	Generalized tumors and MDS	PUVA	Progression		D+	7
12	Blastic NK	M/60	Plaque on head	RT	CR	Skin, BM, LN, blood	D+	22
13	Blastic NK	M/74	Generalized plaques and nodules	COP	CR	Skin, BM	D+	12
14	Blastic NK	M/56	Generalized plaques and large tumor on back, focal BM involvement	CHVmP/BV	CR	Skin, BM, CNS	A+	14
15	Myeloid leukemia	M/66	Generalized plaques and tumors, focal BM involvement	Cyt/Daun+MTX(it)	CR	BM, blood, testes, CNS, skin	D+	6
16	Myeloid leukemia	F/94	Large tumor on flank with surrounding papules	RT	CR	Skin, blood	D+	12
17	Myeloid leukemia	M/2	Tumor on the head and MDS	aBMT	CR	No	Ao	37
18	PCD30+LPD	F/89	Solitary nodule neck	None	CR	No	Do	16
19	PCD30+LPD	F/9	Papules on both arms	None	CR	Skin	A+	84
20	SCPLTCL	M/12	Plaques and nodules arms	Prednisone	PR	Skin, axillary LN	A+	22
21	Per. T NOS	F/67	Localized ulcerating plaques on the face	RT	CR	Skin	D+	66
22	Per. T NOS	F/75	Generalized tumors	CHOP	CR	Skin	A+	35
23	Per. T NOS	M/66	Solitary nodule arm	RT	CR	Skin	D+	22

Nasal NK/T, nasal NK/T-cell lymphoma; nasal-type NK/T, nasal-type NK/T-cell lymphoma; blastic NK, blastic NK-cell lymphoma; NK, natural killer; PCD30+ LPD, primary cutaneous CD30+ lymphoproliferation; SCPLTCL, subcutaneous panniculitis-like T-cell lymphoma; Per. T NOS, peripheral T-cell lymphoma not otherwise specified; M, male; F, female; MDS, myelodysplastic syndrome; RT, radiotherapy; CR, complete remission; PR, partial remission; NR, no response; Ao, alive in complete remission; A+, alive with lymphoma/leukemia; Do, died of unrelated disease; D+, died of lymphoma; CNS, central nervous system; BM, bone marrow; LN, lymph node; C(H)OP, cyclophosphamide, (doxorubicin), vincristin, prednisone; PUVA, photochemotherapy; CHVmP/BV, cyclophosphamide, doxorubicin, teniposide and prednisone, with bleomycin and vincristine added at mid-cycle; Cyt/Daun+ MTX(it), cytarabin, daunorubicin and intrathecal methotrexate; aBMT, autologous bone marrow transplant.

lesions. Treatment mostly consisted of multiagent chemotherapy (n=26; 68%) and resulted in a complete remission in 10 of 40 cases. Only 3 cases did not relapse and 29/38 (76%) died of lymphoma. The prognosis was poor with a median survival of only 6 months (CI: 2-10 months) and a 2-year-survival of 28% (see TABLE **4**). Four cases were of T-cell origin as proved by TCR-analysis.

Univariant analysis showed that only presentation with skin-limited disease (p=0.006) and presentation with localized as opposed to multifocal skin lesions (p=0.05) were associated with a significantly better prognosis. In multivariant analysis only presentation with skin-limited disease was significantly related to a better survival (p=0.03), RR 2.7; CI: 1.1-6.4. The median survival of patients presenting with skin-limited disease was 27 months (CI: 9-45 months) compared to 4 months (CI: 3-5 months) for patients presenting with both cutaneous and extracutaneous disease (see FIGURE **1**)

Table 2. Histological and immunophenotypical data of 23 new patients

Case	Diagnosis	TCR	CD3s	CD2	CD3e	CD4	CD5	CD7	CD8	TIA-1	EBV	CD68	CD30	Other	Histology
1	Nasal NK/T	ND	–	ND	+	–	ND	ND	–	+	+	–	–		Diffuse
2	Nasal-type NK/T	ND	ND	+	+	+	–	ND	–	ND	+	–	–		Angiocentric
3	Nasal-type NK/T	ND	ND	+	+	+	–	ND	–	+	–	–	–	GrB+	Angiocentric
4	Blastic NK	Germ	–	–	–	–	–/+	–	+	–	–	–	–	TdT+	Diffuse
5	Blastic NK	ND	–	–	–	+	–	+/–	–	–	–	+/–	–	TdT+	Diffuse
6	Blastic NK	ND	–	+	+	+	ND	ND	–	–	–	–	–	TdT+	Diffuse
7	Blastic NK	ND	–	+	–	+	ND	ND	–	–	–	–	–	TdT+	Diffuse
8	Blastic NK	Germ	–	+	–	–	–	ND	–	–	–	–	–	TdT+	Diffuse
9	Blastic NK	ND	–	–	–	+	ND	ND	–	–	–	–	–	TdT+	Diffuse
10	Blastic NK	ND	–	–	–	+	–	ND	–	–	–	–	–	ND	Diffuse
11	Blastic NK	ND	–	+	–	+	–	–	–	–	–	–	–	TdT+	Diffuse
12	Blastic NK	ND	–	ND	–	+	–	+	–	–	–	–	–	TdT+	Diffuse
13	Blastic NK	ND	–	+	–	+	–	–	–	–	–	–	–	TdT+	Diffuse
14	Blastic NK	ND	–	+	–	+	–	–	–	–	–	–	–	TdT+	Diffuse
15	Myeloid leukemia	ND	–	–	–	+	–	–	–	–	–	+	–	MPO+	Diffuse
16	Myeloid leukemia	ND	–	–	–	+	ND	–	–	–	–	+/–	–	Lys+/–	Diffuse
17	Myeloid leukemia	ND	–	ND	–	+	ND	ND	–	–	–	+	–	TdT+, MPO+	Diffuse
18	PCD30+ LPD	ND	+	ND	+	+	ND	ND	–	ND	–	–	+		Diffuse
19	PCD30+ LPD	ND	+	+	+	–	+	+	+	+	–	–	+	GrB+	Diffuse
20	SCPLTCL	ND	+	ND	+	–	ND	ND	+	+	–	–	–	GrB+	Subcutaneous
21	Per. T NOS	ND	–	ND	+	–	ND	ND	+	+	–	–	–	GrB+	Epidermotropic
22	Per. T NOS	ND	+	+	+	–	–	ND	+	+	–	–	–	GrB+	Epidermotropic
23	Per. T NOS	ND	+	ND	+	–	ND	ND	–/+	+	–	–	–	GrB+	Subcutaneous

Nasal NK/T, nasal NK/T-cell lymphoma; nasal-type NK/T, nasal-type NK/T-cell lymphoma; blastic NK, blastic NK-cell lymphoma; NK, natural killer; PCD30+ LPD, primary cutaneous CD30+ lymphoproliferation; SCPLTCL, subcutaneous panniculitis-like T-cell lymphoma; Per. T NOS, peripheral T-cell lymphoma not otherwise specified; TCR, T-cell rearrangement; CD3s, CD3 staining on frozen material; CD3e, CD3 staining on parafin-embedded material; EBV, Epstein–Barr virus; TdT, terminal deoxynucleotidyl transferase; MPO, myeloperoxidase; Lys, lysozyme; GrB, granzyme B; +, positive; –, negative; –/+, scattered positive (<25%); +/–, partly (>25%) positive; ND, not done.

Comparison between nasal and nasal-type NK T-cell lymphoma

When comparing these groups of nasal and nasal-type NK/T-cell lymphomas, there were no differences in expression of T-cell related antigens (CD2, CD3, CD4, CD5, CD7 and CD8), CD30-expression, clonality and histology/angiocentricity (see TABLE 3). EBV-expression was present in 100% and 76% of the nasal and nasal-type lymphomas, respectively (p=0.05) After exclusion of 17 nasal-type NK/T-cell lymphomas presenting with only skin lesions (median survival 27 months, CI: 12-42 months), no difference in survival was found between 15 nasal cases (median survival 5 months; CI: 3-7 months) and 23 nasal-type cases (median survival 4 months; CI:3-5 months), see FIGURE 1.

Blastic NK-cell lymphoma (n=63)

This group consisted of 41 male and 20 female cases (male:female ratio=2:1), 2 cases were of unknown gender. The median age at diagnosis was 67 years (range 8-89 years); 13 cases were younger than 40 years. A strikingly high percentage of patients had bone marrow involvement: 46% at presentation and 72% in the course of the disease (see TABLE 3). Initial treatment

Table 3. Relative frequency of expression of various antibodies for different types of CD56+ lymphoma/leukemia, numbers in parentheses denote the number of cases tested

	Nasal NK/T (*n*=15) [% (*n*)]	Nasal-type NK/T (*n*=38) [% (*n*)]	Blastic NK (*n*=63) [% (*n*)]	Myeloid leukemia (*n*=10) [% (*n*)]	CD30+ LPD (*n*=14) [% (*n*)]	SCPLTCL (*n*=6) [% (*n*)]	Per. T NOS (*n*=7) [% (*n*)]
TCR+	14 (14)	14 (28)	0 (60)	0 (8)	71 (14)	100 (5)	100 (4)
EBV	100 (15)	68 (35)	0 (63)	0 (10)	0 (13)	20 (5)	0 (6)
Tia-1/GrB	100 (8)	89 (28)	7[a] (57)	33[a] (9)	70 (10)	100 (5)	100 (5)
CD30	27 (11)	25 (24)	2[a] (42)	0 (6)	100 (16)	0 (3)	0 (5)
CD3s	15 (13)	7 (28)	0 (58)	0 (9)	70 (10)	100 (4)	100 (4)
CD3e	92 (12)	80 (35)	7 (62)	22 (9)	86 (14)	80 (5)	83 (6)
CD4	20 (10)	36 (28)	92 (61)	90 (9)	36 (11)	60 (4)	33 (6)
CD8	10 (10)	12 (26)	2[a] (43)	0 (9)	9 (11)	17[a] (6)	83 (6)
CD2	57 (7)	67 (18)	28 (39)	44 (9)	67 (6)	50 (4)	100 (3)
CD5	0 (5)	7 (14)	2[a] (50)	0 (6)	40 (5)	25 (4)	50 (2)
CD7	50 (6)	33 (12)	24 (29)	27 (8)	40 (5)	50 (4)	33 (3)
TdT	ND	0 (2)	47 (45)	67 (6)	0 (1)	ND	ND
CD34	0 (1)	0 (8)	7 (40)	33 (6)	0 (1)	ND	ND
CD68	0 (4)	0 (13)	41 (44)	81 (7)	0 (8)	67[a] (3)	0 (3)
CD33	0 (1)	0 (2)	0 (39)	100 (7)	0 (1)	ND	0 (1)
MPO	0 (2)	0 (6)	0 (38)	17 (7)	0 (3)	ND	ND
Lysozyme	0 (2)	0 (7)	0 (29)	75 (4)	0 (1)	ND	0 (1)
Angio-centricity	73 (15)	77 (30)	10 (41)	20 (9)	63 (15)	33 (3)	67 (6)
Epidermo-tropism	20 (10)	22 (23)	0 (39)	0 (8)	40 (15)	0 (3)	50 (4)

[a]Expression only in a minority of neoplastic cells (<25%).
Nasal NK/T, nasal NK/T-cell lymphoma; nasal-type NK/T, nasal-type NK/T-cell lymphoma; blastic NK, blastic NK-cell lymphoma; NK, natural killer; PCD30+ LPD, primary cutaneous CD30+ lymphoproliferation; SCPLTCL, subcutaneous panniculitis-like T-cell lymphoma; Per. T NOS, peripheral T-cell lymphoma not otherwise specified; TCR, T-cell rearrangement; EBV, Epstein–Barr virus; GrB, granzyme B; CD3s, CD3 staining on frozen material; CD3e, CD3 staining on parafin-embedded material; TdT, terminal deoxynucleotidyl transferase; MPO, myeloperoxidase.

consisted of multi agent chemotherapy in the majority of patients (70%). Most patients had received CHOP or CHOP-like regimens (56%), whereas 8 patients had been treated more aggressively with schemes used in acute leukemias followed by autologous bone marrow or stem cell transplantation. Six of these 8 patients are alive and although the follow-up is mostly short (median, 25 months; range, 6-40 months) they proved to have a significant better prognosis when compared to all other cases (p=0.01) and compared to cases that received adriamycin containing chemotherapy (p=0.04). The prognosis of these lymphomas was poor with a median survival of 14 months, and 2- and 5- year-overall survival of 33% and 6%, respectively (see table 4). Patients presenting with only skin lesions (median survival 21 months, CI: 14-28 months) had a better prognosis than patients presenting with both cutaneous and extracutaneous disease (median survival 12 months, CI: 10-14 months), see FIGURE 2.

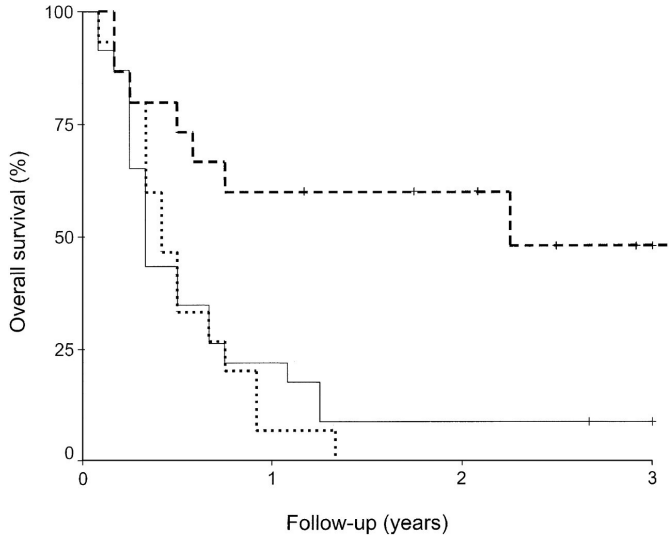

FIGURE 1. Overall survival curves of different groups of nasal(-type) natural killer (NK)/T-cell lymphoma (n = 53) presenting in the skin. Dashed line, nasal-type NK/T (skin lesions only, n = 15); solid line, nasal-type NK/T (skin and extracutaneous localizations, n = 23); dotted line, nasal NK/T (n = 15).

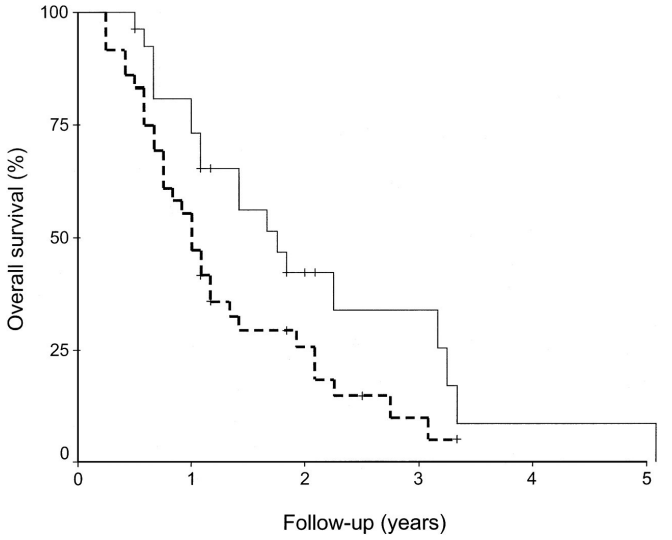

FIGURE 2. Overall survival curves of different groups of blastic natural killer (NK)-cell lymphoma (n = 63) presenting in the skin. Solid line, blastic NK (skin lesions only, n = 27); dashed line, blastic NK (skin and extracutaneous localizations, n = 36).

Univariant analysis showed that the following parameters were associated with a better prognosis: age of 40 or younger (p<0.0001), presentation with only skin lesions (p=0.03), initial treatment with BMT-directed regimens (p=0.01) and TdT expression by more than 50% of the neoplastic cells (p=0,03). Multivariant analysis showed that young age (≤40 years) and TdT expression of more than 50% of the neoplastic cells were both independent prognostic variables (RR of 18.3; CI: 4.2-80.8 and 8.4; CI:2.4-30.0) respectively.

Table 4. Cumulative data for 153 patients with CD56+ lymphomas/leukemias presenting in the skin

	Total	Nasal	Nasal-type	Blastic NK	Myeloid leukemia	CD30+ LPD	SCPLTCL	Per. T NOS
Number	153	15	38	63	10	14	6	7
Male (%)	63	67	56	67	90	42	50	33
Age (years)								
Median	56	58	50	66	52	45	50	67
Range	2–94	19–90	16–79	8–89	2–94	4–89	12–56	28–75
Extent of skin lesions (%)								
Solitary	26	13	25	36	13	25	0	50
Regional	14	7	11	14	25	19	17	17
Generalized	60	80	64	50	62	56	83	33
Presenting localisations (%)								
Skin only	44	0	42	43	30	94	33	100
Nasal-region	10	100	0	2	0	0	0	0
Mouth	1	7	3	2	0	6	0	0
Bone marrow	29	7	23	46	60	0	17[a]	0
Blood	9	0	13	6	30	0	0	0
Lymph node	27	7	18	41	40	6	50	0
Liver	9	13	15	8	0	0	33	0
Spleen	11	13	15	11	10	0	33	0
Lung	4	7	10	2	0	0	0	0
Eye	1	0	5	0	0	0	0	0
Gonads	1	7	0	0	0	0	0	0
Gut	1	0	0	0	10	0	0	0
Bone	1	0	0	0	0	6	0	0
Kidney/adrenal gland	2	7	3	0	10	0	0	0
Other	4	0	10	2	0	0	0	0
Initial therapy (%)								
Radiotherapy	11	13	11	8	10	6	0	33
Multiagent chemotherapy	74	73	70	70	80	44	83	67
Excision	1	0	0	0	0	13	0	0
Puva	1	0	0	2	0	0	0	0
Monochemotherapy	4	0	8	16	0	6	17	0
None	9	13	11	2	10	31	0	0
Result initial therapy (%)								
Complete remission	63	38	42	71	67	85	25	80
Partial remission	12	13	17	8	11	8	50	20
No response/progression	25	50	41	21	22	8	25	0
Relapse (%)								
Skin only	16	0	5	15	25	25	0	50
Systemic	68	100	87	81	55	0	100	33
None	16	0	8	4	30	75	0	17
Follow-up (months)								
Median	12	5	7	13	9	23	6	35
Range	1–84	1–16	1–47	3–61	2–37	2–84	1–25	12–80
Current status (%)								
No evidence of disease	15	0	15	8	30	50	0	14
Alive with disease	12	0	10	13	0	25	17	29
Died of lymphoma	73	100	75	79	70	19	83	57
Died of other cause	1	0	0	0	0	6	0	0
Survival (%)								
5 years	12	NR	NR	6	NR	56	NR	55
2 years	34	NR	28	33	20	75	33	83
Median survival in months (CI)	12 (9–15)	5 (3–7)	6 (2–10)	14 (10–18)	6 (0–13)	NR	5 (1–9)	66 (32–100)

[a]Hemophagocytic syndrome.

Nasal NK/T, nasal NK/T-cell lymphoma; nasal-type NK/T, nasal-type NK/T-cell lymphoma; blastic NK, blastic NK-cell lymphoma; NK, natural killer; PCD30+ LPD, primary cutaneous CD30+ lymphoproliferation; SCPLTCL, subcutaneous panniculitis-like T-cell lymphoma; Per. T NOS, peripheral T-cell lymphoma not otherwise specified; NR, not reached; CI, confidence interval.

CD56+ Myeloid leukemia first presenting in the skin(n=10)

This group included 7 males and 3 females with a median age of 54 years (range 2-94). Seven of 10 cases presented simultaneously with skin lesions and bone marrow and/or blood involvement. The other 3 cases presented with only skin lesions, but developed frank leukemia after 3-12 months. Initial treatment, including CHOP-like courses in 3 cases and AML-schemes in 4 cases, resulted in complete remissions in 6/10 cases. The prognosis was poor with a median survival of 6 months and a 2-year-survival of 20% (see TABLE 4).

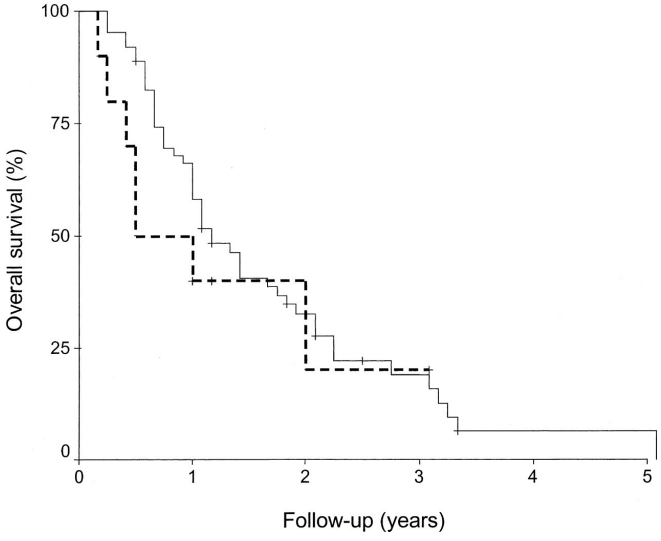

FIGURE 3. Overall survival curves comparing blastic natural killer (NK)-cell lymphoma and myeloid leukemia presenting with skin localizations (n = 73). Solid line, blastic NK (n = 63); dashed line, CD56+ myeloid leukemia presenting on the skin (n = 10).

Comparison between blastic NK cutaneous CD56+ myeloid leukemia

In view of recent reports that blastic NK and a proportion of myeloid leukemias, presenting in the skin are possibly derived from precursor plasmacytoid dendritic-cells type 2 [46,62,64], we compared the 63 cases diagnosed as blastic NK to the ten CD56+ myeloid leukemias. Striking similarities between both groups were noted in histology, immunophenotype, including expression of CD34, CD68 and TdT (but with the exception of CD33, myeloperoxidase and lysozyme used as exclusion criteria for blastic NK). Clinical presentation, including the percentage of bone marrow involvement at presentation (46% versus 60%), response to therapy and prognosis (see TABLE 4 and FIGURE 3).

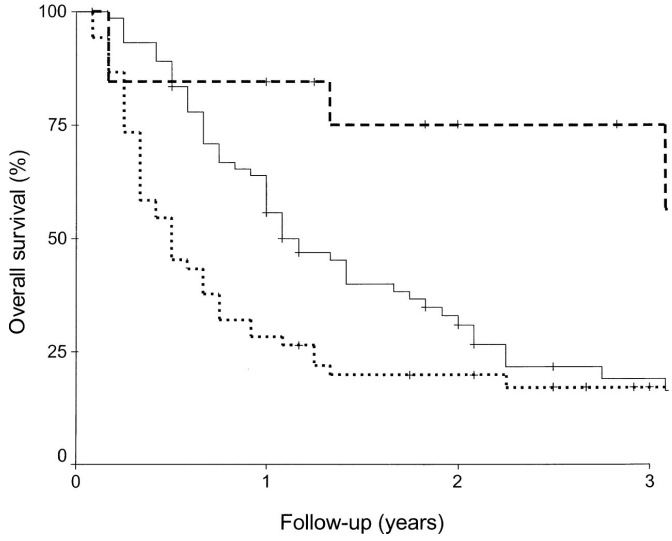

FIGURE 4. Overall survival curves of the main groups of CD56+ lymphomas/leukemias presenting in the skin (n = 140). Dashed line, cutaneous CD30+ lymphoproliferation (n = 14); solid line, blastic natural killer (NK)/CD56+ myeloid leukemia (n = 73); dotted line, nasal(-type) NK/T (n = 53).

Cutaneous CD30+ Lymphoproliferations with CD56 expression (n=14)

This group consisted of 5 males, 8 females and 1 case with unknown gender. The median age was 45 years (range 4-89). The group included 10 primary cutaneous CD30+ large cell lymphomas, including 6 cases designated previously CD56+ NK/NK-like T-cell lymphoma with expression of CD30 antigen, 3 cases of LyP and one case of anaplastic (ALK-positive) CD30+ lymphoma presenting with lesions in the skin, bone, lymph nodes and parotis.
Initial therapy consisted of multi agent chemotherapy in 6/14, whereas five cases were not treated at all. Three cases died, two of them within 2 months, due to side effects of chemotherapy, and one of unrelated disease. The median survival was not reached; the 2 and 5-year-survival were 75% and 56%, respectively.

Subcutaneous panniculitis-like T-cell lymphoma (n=6)

This group consisted of 3 males and 3 females, the median was 50 years (range 12-56 years). Two cases presented with solely skin lesions, whereas 3 cases had concurrent involvement of lymph nodes. Chemotherapy resulted in a complete remission in only one of six patients, and all but one died of lymphoma. The median survival was only 5 months (CI: 1-9 months); the 2-year-survival was 33% (see TABLE **4**). The only patient still alive had an alpha/beta phenotype, whereas the other 5 patients who died had a gamma/delta phenotype.

Peripheral T-cell lymphoma not otherwise specified (n=7):

This group consisted of 2 males, 4 females and 1 case with unknown gender. The median age was 67 years (range 28-75 years). All cases presented with skin lesions only. It was a heterogenous group, including 4 epidermotropic CD8+ CTCL[63], two CD30- large primary cutaneous T-cell lymphomas[3], and one large granular NK/T-cell leukemia with skin localizations. Initial treatment resulted in a complete remission in four cases, but all but one patient relapsed. Four of seven patients died of lymphoma. The median survival was 66 months (CI: 32-100 months); the 2 and 5-year-survival were 83% and 56%, respectively.

Discussion

In the present study 153 CD56+ lymphomas and leukemias, first presenting in the skin and with a minimum follow-up of 12 months or prior death to lymphoma, were evaluated. This group included 23 new cases and 130 cases retrieved from literature. The goals of this study were to assess whether the different groups of CD56-positive lymphomas recognized in the WHO classification differ in clinical behaviour, to define prognostic parameters and to deduct guidelines for diagnosis and treatment. In general these CD56+ lymphomas/leukemias had a poor prognosis with a median survival of 13 months. After a median follow-up of 12 months only 27% of patients alive with or without disease. Survival curves of the main groups of cutaneous CD56+ lyphomas/leukemias are presented in FIGURE **4**.

Blastic NK-cell lymphomas were by far the largest group (63 of 157 cases; 40%). In recent literature such cases have had been designated variously as blastic or blastoid NK-cell lymphoma and (haematodermic) CD4+/CD56+ leukemia/lymphoma[2,18,23,46]. These patients had a poor prognosis with a median survival of only 14 months. CHOP(-like) courses may result in initial complete remissions in these patients, but quick relapses unresponsive to further chemotherapy are characteristic of these tumors. Multivariate analysis revealed that age ≤40 years and high expression of TdT by the neoplastic cells were independently associated with a better prognosis. Young patients treated with aggressive regimens used in acute leukemias had a better prognosis than patients treated with CHOP(-like) regimens[6,18,29,30,48,59]. Further studies are necessary to confirm these findings and to find out if more aggressive therapies are also superior in older patients.

Comparison between blastic NK-cell lymphomas and CD56+ myeloid leukemias presenting in the skin showed striking similarities in histology, immunophenotype, clinical presentation, including the percentage of bone marrow involvement at presentation (46% compared to 60%) and prognosis. Also in a recent workshop of the EORTC Cutaneous Lymphoma Study group on cutaneous CD56+ lymphomas the great similarities between both groups were noted (Muche et al, in preparation). These observations suggest that these two conditions are closely related. In addition, the development of acute myeloid leukemia in patients with blastic NK-cell lymphoma has been reported[28].

Recent studies demonstrated that blastic NK-cell lymphomas express markers typical of plasmacytoid dendritic cells, in particular the IL-3R alpha chain (CD123) and the lymphoid proto-oncogene TCL1 [62]. Expression of CD123 has also been reported in a proportion of myeloid leukemias presenting in the skin[46,64].

The overlapping clinical, histological and immunophenotypical features of blastic NK-cell lymphoma and CD56+ myeloid leukemias presenting in the skin provide also a rationale to treat these patients with more aggressive regimens used in myeloid leukemias rather than with convential CHOP(-like) regimens. Moreover, the term blastic NK-cell lymphoma is probably a misnomer, because the disease is neither of NK-cell origin nor a lymphoma.

Nasal and nasal-type NK/T-cell lymphomas together represented the second largest group in this study (55 of 157 cases; 35%). In cases with a true T-cell phenotype as defined by expression of surface CD3 and/or the presence of a clonal TCR gene rearrangement, which express cytotoxic proteins, but no EBV, it is arbitrary to decide whether a diagnosis of nasal-type NK/T-cell lymphoma or peripheral T-cell lymphoma not otherwise specified (NOS) should be made. In this study such EBV-negative cases were classified as PTL, NOS. Angiocentricity proved not very helpful in distinguishing both groups, because this feature was observed in all groups investigated in this study (see TABLE 3). Nasal and nasal-type NK/T-cell lymphoma

showed many similarities (see TABLE **4**). No difference in survival was found between nasal NK/T-cell lymphomas (presenting with concurrent cutaneous disease) and nasal-type NK/T-cell lymphomas presenting with cutaneous and extracutaneous disease (median survival 5 and 4 months, respectively). Nasal-type NK/T-cell lymphomas presenting with skin-limited disease had a somewhat better prognosis, which is consistent with the results of previous studies in primary cutaneous angiocentric lymphomas[65](see figure 1). The poor survival data in these nasal (type) NK/T-cell lymphomas also indicate that current standard regimens, -generally doxorubicin-based chemotherapy-, are insufficient in these cases, and that other approaches should be investigated.

Apart from the entities discussed above, other types of CTCL can occasionally show co-expression of CD56. Within the group of CD56+ SCPLTCL 5 of 6 cases appeared to have a gamma/delta phenotype. These gamma/delta-positive cases are often not confined to the subcutis, but may extend into the dermis66. In such cases differentiation between SCPLTCL and nasal-type NK/T-cell lymphomas extending into the subcutis may be difficult[12]. Noteworthy, both groups have a similar poor prognosis, and do not respond sufficiently to CHOP(-like) therapy. The only patient with a CD56+ SCPLTCL still alive in this study had a alpha/beta T-cell phenotype. This observation is consistent with the results of other studies indicating that SCPLTCL with an alpha/beta phenotype have a much better prognosis than cases with a gamma/delta phenotype, and that both groups should be considered separately[49,67]

Previous studies in systemic CD30+ anaplastic large cell lymphoma suggested that expression of CD56 is associated with a more unfavorable prognosis68. The favourable prognosis of the patients with a primary cutaneous CD30+ lymphoma and LyP included in this study suggests that CD56 expression does not affect clinical behaviour and outcome in the group of primary cutaneous CD30+ lymphoproliferations. Similarly, the four cases with an epidermotropic CD8+ CTCL, with co-expression of CD56 did not differ clinically from CD56- cases, described previously[63].
Classification of lymphomas which are defined primarily by phenotype, such as these CD30+ lymphomas and CD8+ CTCL, and which at the same time express CD56 may be difficult. This problem is well illustrated by the 8 CD30+/CD56+ lymphomas in the study of Mrasz et al.[38]. In that study on NK/NK-like T-cell lymphoma, primarily defined by the presence of CD56 expression, it was found that cases that co-express CD30 had a much better prognosis than CD30-negative cases. Seven of eight cases are alive and well after initial treatment and did not relapse. It seems that these patients have a clinical presentation and course similar to that observed in primary cutaneous CD30+ CTCL[7,69]. Although EBV-expression was noted in 3/8 cases, one wonders why at least some of the cases were not simply classified as primary cutaneous CD30+ CTCL with co-expression of CD56. Therefore, studies on larger number

of patients with co-expression of CD30 and CD56 are necessary. If confirmed that primary cutaneous CD30+ CTCL with co-expression of CD56 do not have another clinical behaviour than CD56-negative cases, cases with localized disease can better be treated with radiotherapy than multi agent chemotherapy.

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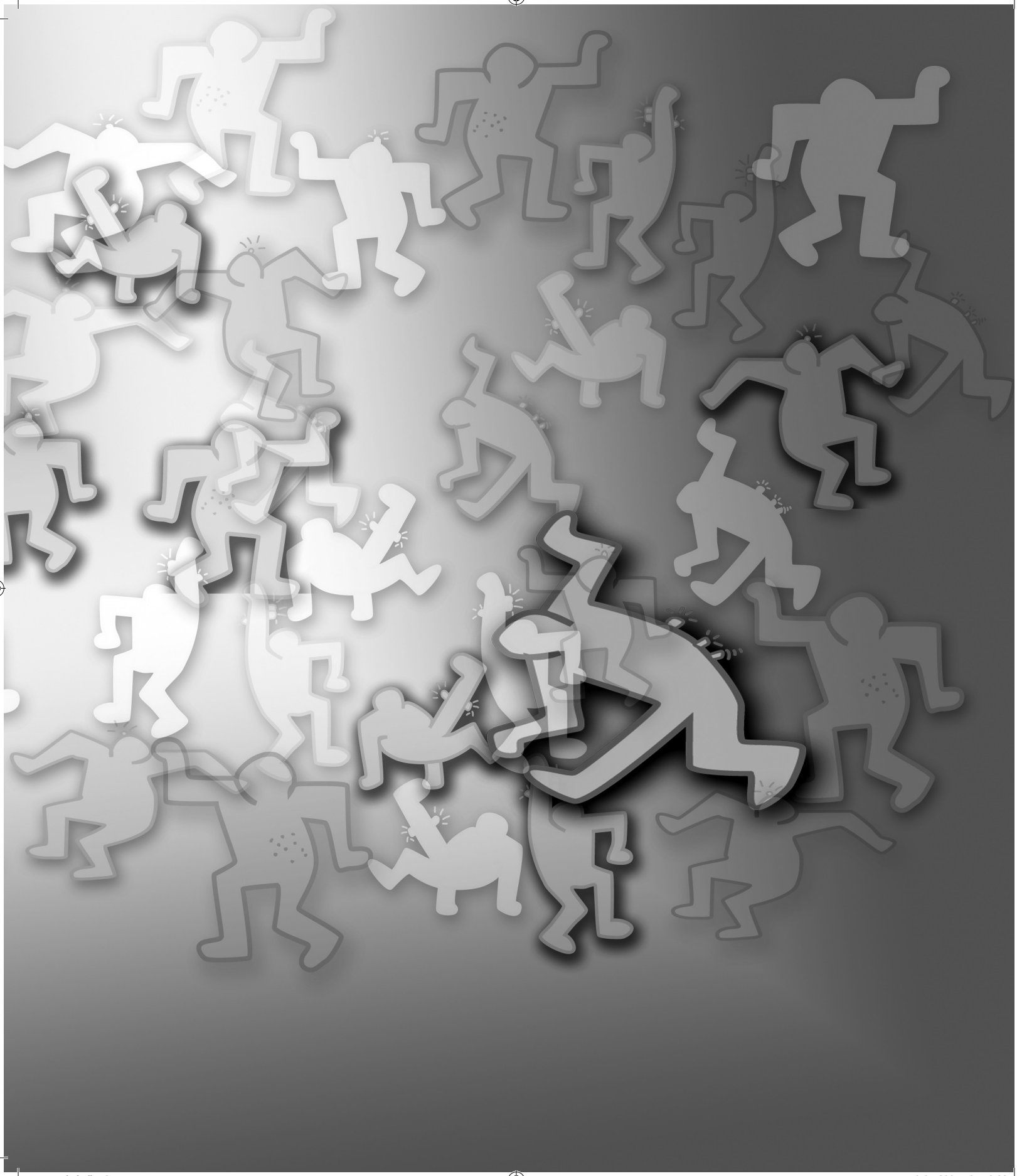

chapter 5

Lymphomatoid papulosis with a natural killer-cell phenotype

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Marcel W. Bekkenk [1]
Philip M. Kluin [2]
Patty M Jansen [2]
Chris JLM Meijer [2]
Rein Willemze [1]

1. Department of Dermatology, Leiden University Medical Center, the Netherlands
2. Department of Pathology, Leiden University Medical Center, the Netherlands

Abstract

Lymphomatoid papulosis (LyP) is defined as a recurrent self-healing papulonodular eruption with the histological features of a (CD30+) cutaneous T-cell lymphoma. The atypical cells usually have a CD3+/-, CD4+/-, CD8-, CD30+, CD56- T-cell phenotype. We report an unusual case of LyP, in which the atypical cells expressed a CD3-, CD4-, CD8-, CD30+, CD56+ phenotype. Detailed phenotypic and genotypic analysis confirmed that these cells had a natural killer NK-cell phenotype. Lymphomas with an NK-cell phenotype usually have a poor prognosis. However, the waxing and waning of papular lesions for more than 20 years and the excellent response to low-dose oral methotrexate in this patient suggest similar clinical behaviour to LyP cases with a T-cell phenotype.

Introduction

Lymphomatoid papulosis (LyP) is characterized by a chronic recurrent, self-healing papulonodular skin eruption with histological features of a (CD30+) cutaneous T-cell lymphoma.[1,2] Characteristically, the skin lesions show a wedge-shaped to diffuse dermal infiltrate with variable numbers of CD30+ large, often anaplastic cells in a background of inflammatory cells. These atypical cells normally express a T-cell phenotype with variable loss of pan-T antigens (CD2, CD3, CD5, CD7). Most cases have a CD4+ T-cell phenotype, whereas only some cases express a CD8+ T-cell phenotype.[3] Expression of CD15 is rare. We describe a patient with LyP in whom the atypical cells expressed a natural killer (NK) -cell phenotype. Whereas CD56+ NK-cell lymphomas usually have a poor prognosis, the disease in this patient showed a chronic indolent clinical course characteristic of LyP. Additional studies in another 10 patients with LyP and 10 patients with a primary cutaneous CD30+ large T-cell lymphoma (LTCL) showed expression of CD56 in two of 20 cases, both with a T-cell phenotype.

Case report

A 47-year-old white man was referred with a 20-year history of generalized papular skin lesions that had been treated with various topical steroids without effect. The lesions always disappeared spontaneously after 6-8 weeks, but new lesions appeared at other sites simultaneously. His general medical history revealed diabetes mellitus type II and a myocardial infarction. His medication consisted of acetylsalicylic acid, an angiotensin-converting enzyme inhibitor and tolbutamine. On examination, dozens of papular and papulonodular lesions were observed on the trunk, arms and legs, sparing the head. On the abdomen the papular lesions coalesced to form a large plaque (**Fig. 1**). A tumorous lesion of 3 cm diameter had recently developed on the right leg (**Fig. 2**). No lymphadenopathy or hepatosplenomegaly was found.

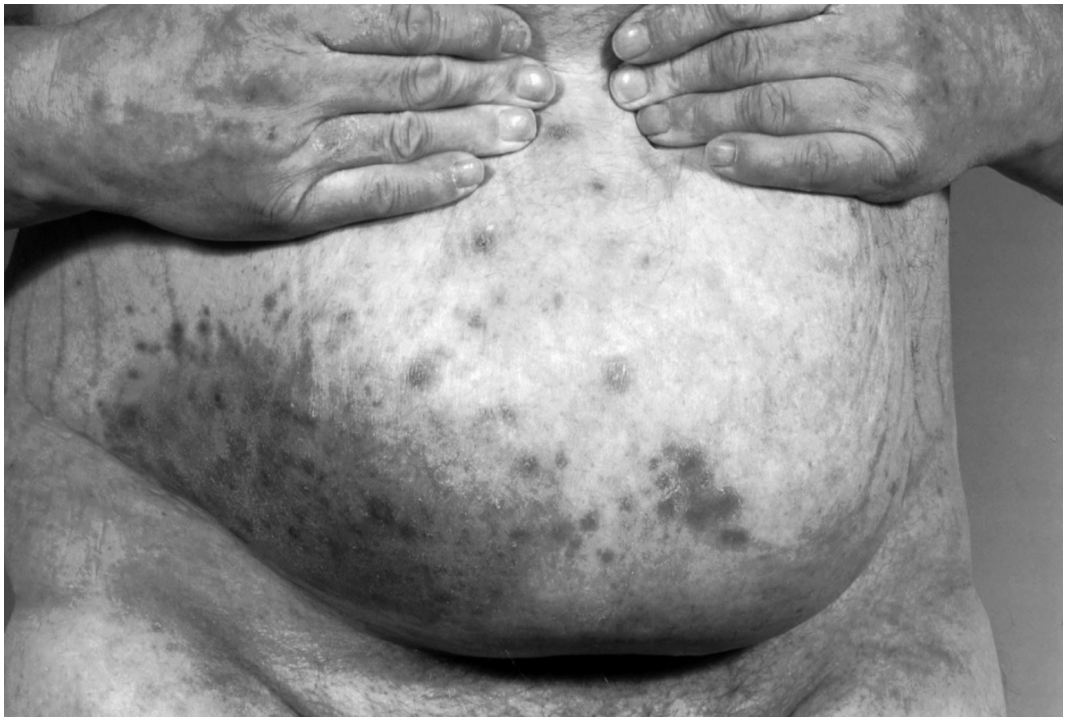

FIGURE 1. Numerous papular lesions coalescing to form a large plaque on the abdomen

Histological and immunohistochemical analysis

Histological evaluation of the tumorous lesion on the right leg and of a fully developed papule on the abdomen showed essentially the same picture. Both lesions showed a diffuse, non-epidermotropic infiltrate containing clusters of large anaplastic cells with a considerable admixture of small T-cells, histiocytes and small clusters of B-cells (**FIG. 3A**). The atypical cells strongly expressed CD30, CD43 and CD56, but were negative for CD2, CD3 and leu4, CD4, CD5, CD7, CD8, CD15, CD20, CD34, CD57, CD68, lysozyme, myeloperoxidase, anaplastic lymphoma kinase (ALK, p80), granzyme B, TIA-1 and F-1 (**FIG. 3B-D**). Analysis for Epstein-Barr virus (EBV)-encoded RNA and latent membrane protein-1 did not show the presence of EBV. Analysis of T-cell receptor (TCR)- gene rearrangement using the heteroduplex polymerase chain reaction 4 did not identify a T-cell clone. Taken together, these results are consistent with a NK-cell phenotype of the neoplastic cells.

Clinical course

Because of this unusual phenotype and the extent and size of the skin lesions, routine staging procedures, including thoracic and abdominal computed tomographic scan, bone marrow biopsy, blood analysis and an examination by an ear/nose/throat specialist were performed, but these failed to demonstrate extracutaneous involvement. Clinical observation during

hospitalization confirmed the recurrent, self-healing nature of the skin lesions. Based on a combination of the clinical picture of recurrent self-healing skin lesions with the histological picture of a CD30+ lymphoproliferation the diagnosis LyP was made. When treatment with low-dose oral methotrexate (22·5 mg weekly) was instituted, no further lesions developed and the existing lesions slowly resolved. Methotrexate was tapered off and our patient remains free of skin lesions on a maintenance dose of 10 mg weekly.

Evaluation of 20 primary cutaneous CD30+ lymphoproliferations for CD56 expression

To evaluate the frequency of CD56 expression in primary cutaneous CD30+ lymphoproliferations the phenotype of 10 other patients with LyP and 10 patients with a primary cutaneous CD30+ LTCL was analysed. Only one of 10 patients with LyP and one of 10 with primary cutaneous CD30+ LTCL expressed CD56. Both were of T-cell phenotype [CD3+(leu4)/CD4-/CD8+ and CD3+(leu4)/CD4+/CD8-,respectively,].There was no difference in clinical behaviour in these two patients as compared with CD56- cases.

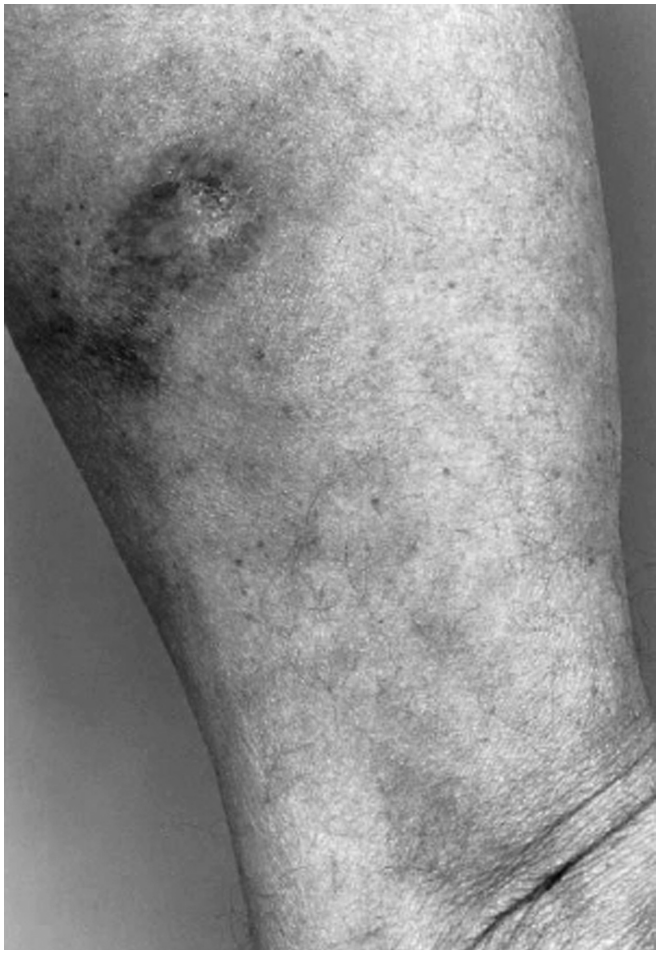

Figure 2. Tumerous lesion on the right leg.

Discussion

The CD56 marker reactive with the neuronal cell adhesion molecule is a marker for NK-cells. Owing to the recent availability of an anti-CD56 monoclonal antibody reactive on paraffin-embedded tissue (clone 123C3),[5] several types of non-Hodgkin's lymphoma with NK/T-cell phenotype have been recognized.[6] Nasal NK/T-cell lymphoma, previously known as lethal midline granuloma, usually expresses CD56 and is considered to be the prototype of NK-cell lymphoma.[7] It has a

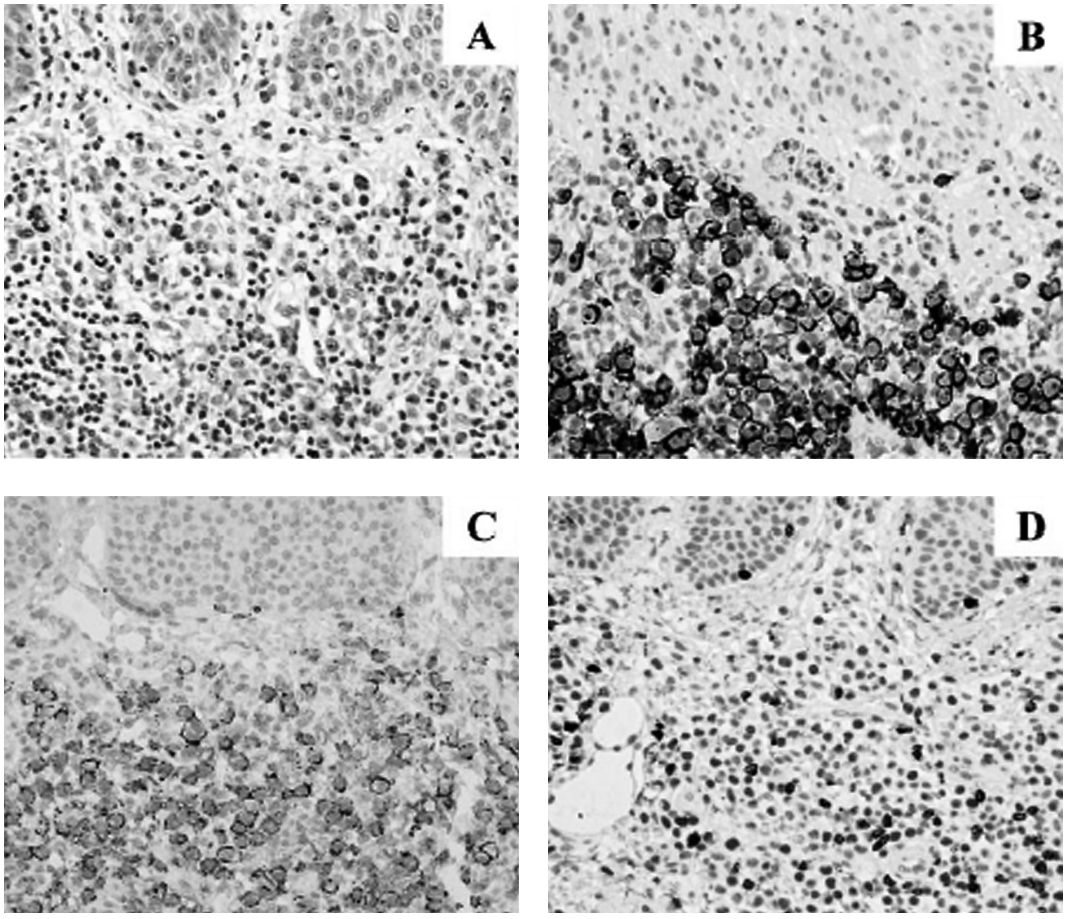

Figure 3. (A) Histological evaluation of a papular lesion showing an atypical diffuse non-epidermotropic infiltrate (haematoxylin and eosin). The atypical cells express CD30 (B), CD56 (C), but not CD3 (D). Original magnification 200x.

strong association with EBV and is more frequent in Asia and South and Central America.[6,7] Lymphomas with similar histological and immunohistochemical features presenting at other, mostly extranodal, sites are described as NK/T-cell lymphoma of nasal-type.[8,9] The association with EBV in this type is variable. More recently, a subtype with a monotonous infiltrate of medium to large sized blasts with an NK/T-cell phenotype designated blastoid NK-cell lymphoma has been reported.[8,10,11] This type of lymphoma is not associated with EBV and differentiation from skin localizations of acute myeloid leukaemia (AML) may be extremely difficult,[12] as AML can also express CD56. Differentiation is especially difficult if blood and bone marrow involvement cannot be demonstrated (aleukaemic leukaemia cutis). In addition to the three above-mentioned NK/T-cell lymphoma subtypes, several other well-defined types of lymphoma can coexpress CD56, such as subcutaneous panniculitis-like T-cell lymphoma[13] and CD30+ anaplastic large cell lymphomas.[14-17]

This report describes the first patient with LyP expressing CD56. Detailed immunophenotypical and genotypical analysis indicated that the atypical cells in this patient were of true NK-cell origin rather than T-cells coexpressing CD56. The absence of TCR- chain gene rearrangement cannot be attributed to under-representation of too low a number of CD30+/CD56+ atypical cells, as these constituted approximately 50% of the total number of cells in the dermal infiltrate. Clinically the patient showed classical features of LyP, with a history of 20 years of waxing and waning of papulonodular lesions. Whereas staging is usually not indicated in patients with LyP, we decided to stage this particular patient because of the extent and size of the skin lesions, the uncertainty at the first visit whether there was complete clearance of all individual lesions, and in particular the uncommon phenotype of the atypical cells, given that CD56+ non-Hodgkin's lymphomas are usually associated with a poor prognosis. After exclusion of extracutaneous disease he was treated with low-dose methotrexate (22·5 mg weekly), which resulted in almost immediate cessation of the development of new lesions and the slow clearing of the existing lesions. Methotrexate was tapered off to 10 mg weekly, but no new lesions have appeared.

Recent studies have indicated that CD56 expression is an independent marker of poor prognosis in both ALK+ and ALK-CD30+ anaplastic large cell lymphoma.[16] Moreover, a recent report described a patient with a primary cutaneous CD30+ anaplastic large cell lymphoma coexpressing CD56 who did not respond to systemic chemotherapy.[15] It was suggested that coexpression of CD56 might identify a subset of primary cutaneous CD30+ lymphomas with a more aggressive clinical behaviour.[15] To find out if coexpression of CD56 may be considered as a prognostic marker in the group of primary cutaneous CD30+ lymphoproliferations, CD56 expression was evaluated in 10 additional cases of LyP and 10 cases of primary cutaneous CD30+ LTCL. Coexpression of CD56 was found in one of 10 patients with LyP and one of 10 patients with primary cutaneous CD30+ LTCL. Both cases showed a mature CD3+ (leu4)/CD4+ /CD8- or CD3+ (leu4)/CD4-/CD8+ T-cell phenotype. Neither of these two patients developed extracutaneous disease during follow-up (14 and 84 months, respectively). This and other studies[14-17] do not suggest that coexpression of CD56 in primary cutaneous CD30+ lymphoproliferations has prognostic significance in contrast to systemic anaplastic CD30+ LTCL.[18] They also indicate that most primary cutaneous CD30+ lymphoproliferations coexpressing CD56 are of T-cell origin (expressing leu4), and that cases with a NK-cell phenotype, as reported here, are exceedingly rare.

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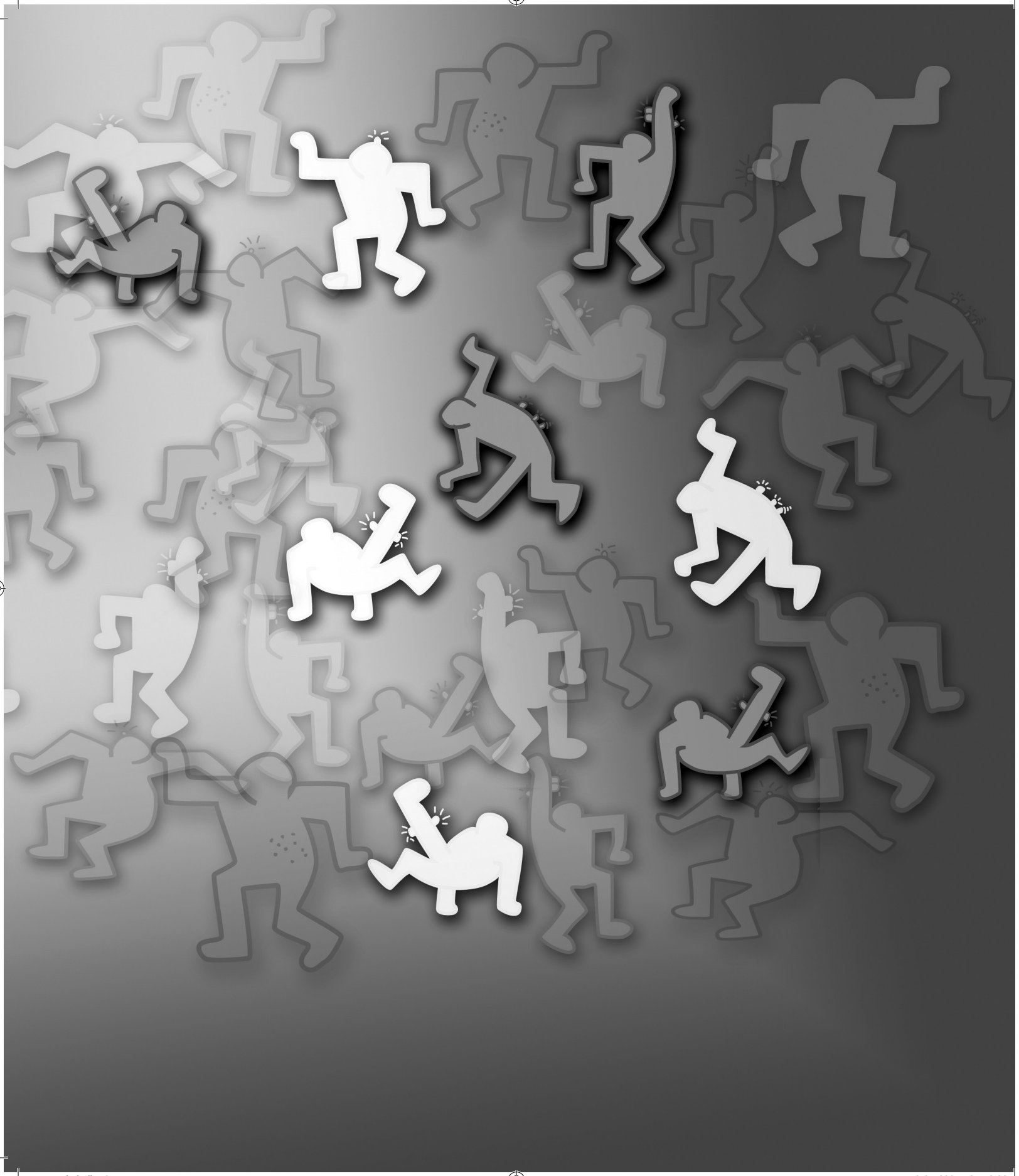

chapter 6

Prognostic factors in primary cutaneous large B-cell lymphomas: a European multicenter study

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F. Grange [1]
Marcel W. Bekkenk [2]
J. Wechsler [3]
L. Cerroni [4]
M. Bernengo [5]
J. Bosq [6]
G. Hedelin [7]
Chris JLM Meijer [8]
R. Fink Puches [4]
W. A. van Vloten [9]
P. Joly [7]
M. Bagot [3]
Rein Willemze [1]

1. Department of Dermatology, Hôpital Pasteur, Colmar, France
2. Department of Dermatology, Leiden University Medical Centre, Leiden, the Netherlands
3. Departments of Pathology and Dermatology, Hôpital Henri-Mondor, Créteil, France
4. Department of Dermatology, University of Graz, Graz, Austria
5. Department of Dermatology, University of Turin, Italy
6. Department of Pathology, Institut Gustave Roussy, Villejuif, France
7. Department of Dermatology, Hôpital Charles Nicolle, Rouen, France
8. Departments of Pathology and Dermatology, Free University Hospital, Amsterdam, the Netherlands
9. Department of Dermatology, University Medical Centre, Utrecht, the Netherlands

Abstract

Purpose

Most primary cutaneous B-cell lymphomas have an excellent prognosis. However, primary cutaneous large B-cell lymphomas (PCLBCLs) of the leg have been recognized as a distinct entity with a poorer prognosis in the European Organization for Research and Treatment of Cancer (EORTC) classification. This distinction on the basis of site has been debated. Our aim was to identify independent prognostic factors in a large European multicenter series of PCLBCL.

Patients and methods

The clinical and histologic data of 145 patients with PCLBCL were evaluated. According to the EORTC classification, 48 patients had a PCLBCL of the leg and 97 had a primary cutaneous follicle center-cell lymphoma (PCFCCL). Data from both groups were compared. Univariate and multivariate analyses of specific survival were performed using a Cox proportional hazards model.

Results

Compared with PCFCCL, PCLBCL-leg were characterized by an older age of onset, a more recent history of skin lesions, a more frequent predominance of tumor cells with round nuclei and positive bcl-2 staining, and a poorer 5-year disease-specific survival rate (52% v 94%; $P < .0001$). Univariate survival analysis in the entire study group showed that older age, a more recent onset of skin lesions, the location on the leg, multiple skin lesions, and the round-cell morphology were significantly related to death. In multivariate analysis, the round-cell morphology ($P < .0001$), the location on the leg ($P = .002$), and multiple skin lesions ($P = .01$) remained independent prognostic factors. The round-cell morphology was an adverse prognostic factor both in PCLBCL-leg and in PCFCCL, whereas multiple skin lesions were associated with a poor prognosis only in patients with PCLBCL-leg.

Conclusion

With site, morphology, and number of tumors taken into account, guidelines for the management of PCLBCL are presented.

Introduction

Primary cutaneous B-cell lymphomas represent a heterogeneous group of B-cell neoplasms, which present in the skin without evidence of extracutaneous disease.[1-8] The majority of these primary cutaneous B-cell lymphomas are large-cell lymphomas (primary cutaneous large B-cell lymphomas [PCLBCLs]).[9] In the European Organization for Research and Treatment of Cancer (EORTC) classification for primary cutaneous lymphomas, two main groups of PCLBCL are distinguished.[6] Most cases are included in the group of primary cutaneous follicle center-cell lymphomas (PCFCCLs). This term was introduced in 1987 [5] as an encompassing term for cutaneous lymphomas that were composed of centroblasts and centrocytes of various sizes and that were classified as either centroblastic/centrocytic or centroblastic lymphomas according to the criteria of the Kiel classification.[10] These PCFCCLs appeared as a well-defined group of primary cutaneous B-cell lymphomas which often presented with skin lesions confined to a limited skin area on the head or the trunk; they had an excellent prognosis, irrespective of the proportion of large cells and the histologic subclassification.[5-8] However, it was noted from the first publications regarding these PCFCCLs that patients presenting with skin tumors on the leg had a different clinical behavior.[5] Since these tumors of the leg were consistently composed of a majority of large B-cells, the term primary cutaneous large B-cell lymphoma of the leg (PCLBCL-leg) was used.[11] Recent studies have demonstrated that patients with PCLBCL-leg differed from patients with PCFCCLs arising at other sites by a higher age of onset, a poorer prognosis, and the almost constant expression of bcl-2 protein.[6,8,11,12] For these reasons, PCLBCL-leg was included as a separate entity in the EORTC classification.[6] Although recent studies have confirmed that these PCLBCL-leg are a distinct group with an intermediate prognosis,[8] the subdivision of primary cutaneous B-cell lymphomas into two main categories (PCLBCL-leg and PCFCCL) primarily based on site of presentation (leg v other sites) has been much disputed.[13-17] Indeed, it remained unknown to what extent site, age, morphology, bcl-2 expression, or other parameters contribute to the difference in survival between these two groups.

This prompted us to perform a large European study of primary cutaneous B-cell lymphomas, including both PCLBCL-leg and PCFCCL with a predominance of large cells (nonleg PCLBCLs). The main goals of this study were (1) to identify independent prognostic factors in the total group of PCLBCLs, (2) to find out whether PCLBCL-leg have indeed a different clinical behavior, and (3) to define additional prognostic parameters within pertinent subgroups of PCLBCL. The ultimate goal of this study was to provide practical guidelines to both pathologists and clinicians that may contribute to appropriate management and treatment of these PCLBCLs.

PATIENTS AND METHODS

The Dutch Cutaneous Lymphoma Working Group, the French Study Group on Cutaneous Lymphomas, and two departments of dermatology from other countries (Graz, Austria, and Turin, Italy) participated in the study.

Inclusion Criteria

Patients included in the registry of one of the participating groups or departments were selected for analysis if they met the following criteria: (1) diagnosis of cutaneous B-cell lymphoma between January 1, 1979, and March 1, 1998; (2) absence of extracutaneous disease detected by a comprehensive staging procedure at diagnosis; and (3) histologic and immunophenotypic features showing a majority (ie, > 50%) of large cells among neoplastic B-cells. The staging procedure at diagnosis included in all cases physical examination, routine laboratory tests, chest radiograph or thoracic computed tomography scan, abdominal ultrasound tomography or abdominal computed tomography scan, and bone marrow cytology (3% of cases), bone marrow histology (8%), or both (89%). One hundred forty-five patients were included in the study. Twenty-three of them had been included in a previous prognostic study.[8] According to the criteria of the Revised European-American Classification of Lymphoid Neoplasms[18] and the World Health Organization classification,[19] all 145 patients were classified as having a diffuse large B-cell lymphoma.

Histologic Review

For each case, hematoxylin-eosin slides and CD3 and CD20 stainings were studied. In addition, bcl-2 expression was studied using formalin-fixed, paraffin-embedded sections deparaffinized and stained with an appropriate monoclonal antibody (clone 124; Dako, Copenhagen, Denmark), when available (55 of 145 cases). The bcl-2 staining was considered positive if

Table 1. Histologic Subclassification: Criteria and Results

	Subgroup*	Criteria*	No.	Final Classification
I	Immunoblastic	> 70% immunoblasts (large cells with a single prominent central nucleolus)	5	
II	Polymorphous centroblastic	Predominance of centroblasts (noncleaved cells with prominent often marginal nucleoli) and immunoblasts > 10% immunoblasts	15	> 50% round (noncleaved) cells, n = 53 (36.5%)
III	Centroblastic	> 50% centroblasts < 10% immunoblasts	30	
IV	Unclassified	Predominance of large noncleaved cells	3	
V	Centroblastic/centrocytic	Variable number of centroblasts and large centrocytes (cleaved cells) 25% < round cells < 50%	23	
VI	Large Centrocytic	> 75% large centrocytes (including multilobated cells) < 25% centroblasts	68	> 50% cleaved cells, n = 92 (63.5%)
VII	Unclassified	Predominance of large cleaved cells	1	

*According to updated Kiel classification with minor modifications.

more than 25% of the neoplastic large cells showed an unequivocal bcl-2 positivity. Cases in which only a minor proportion of tumor cells weakly expressed bcl-2 protein were considered negative. Histologic subclassification was based essentially on the relative proportions of immunoblasts, centroblasts (large noncleaved cells), and large centrocytes (large cleaved cells), including multilobated cells, and all cases were classified into five categories following the criteria of the updated Kiel classification,[10] with minor modifications (**TABLE 1** and **FIG 1**). Because such a detailed subdivision was expected to result in a major interobserver variation, it was decided to distinguish two major subgroups depending on the presence or absence of more than 50% large B-cells with round nuclei. Skin biopsy specimens had first been reviewed separately by four (dermato)pathologists (J.W., C.J.L.M.M., L.C., and R.W.) from different centers who had no knowledge of the clinical data. Next, all cases were reviewed during a special meeting of this pathology panel using a multihead microscope and classified by consensus. The results of this histologic classification are presented in **TABLE 1**.

Reproducibility Study

Since in the course of the study the distinction between cleaved-cell and round-cell PCLBCL appeared as a major independent prognostic parameter, we studied the reproducibility of this simple histologic subclassification in a sample of 38 randomly selected cases. Fourteen cases were reviewed by a panel of six pathologists from the Dutch group and 24 cases were reviewed by a panel of six pathologists from the French group. Participants had not taken part in the previous histologic review. They were asked to classify each tumor into one of the two main categories: cleaved-cell PCLBCL and round-cell PCLBCL. Results were compared with the final histologic classification obtained on the basis of consensus during the histologic review (**TABLE 1**)

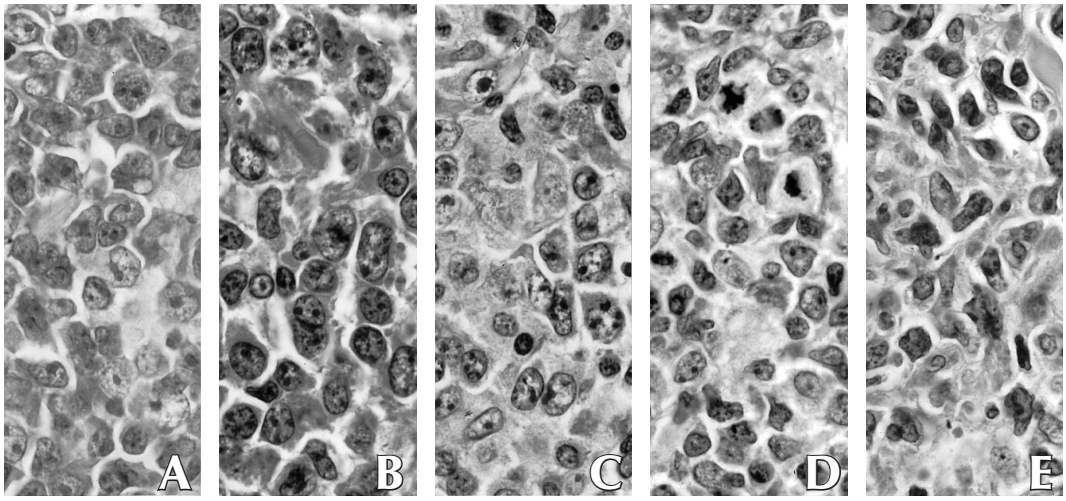

FIGURE 1. Histopathologic features in PCLBCLs (400): (A) round cells, immunoblastic; (B) round cells, polymorphous centroblastic; (C) round cells, centroblastic; (D) cleaved cells, centroblastic/centrocytic; (E) cleaved cells, large centrocytic.

Data Collection

Variables analyzed for prognostic value were as follows: age at diagnosis; sex; anatomic site (head and neck, arm, anterior aspect of the trunk, posterior aspect of the trunk including the buttock, or leg); diameter of the largest skin lesion; number of skin lesions; cutaneous extent ("localized" when either one or multiple skin lesions were restricted to one anatomic site, and "disseminated" when several anatomic sites or several limbs were involved); duration of skin lesions before diagnosis; spontaneous regression of skin lesions; serum lactate dehydrogenase (LDH) level; and histologic group (round-cell v cleaved-cell morphology) as determined by the histologic review. Histories of noncutaneous lymphoma or leukemia, pseudolymphoma, or small-cell primary cutaneous B-cell lymphoma and the presence of B symptoms were registered but were not included in the prognostic analysis because they were observed in too small a number of patients. Bcl-2 protein expression was not included in the prognostic analysis because of insufficient data.

Follow-Up Data

Follow-up information was recorded until December 1, 1998 (end point), and included therapy, achievement of a complete response, relapse, nodal or visceral progression of the disease, status at the end point or last follow-up, and date and cause of death. The follow-up time ranged from 3 to 203 months (median, 41 months; mean, 53 months). A total of 133 patients were followed up until death or until the end point or for a period greater than 5 years. Twelve patients (8%) were lost to follow-up after a duration of 5 years (range, 10 to 59 months).

Statistical Analysis

Comparisons between different subgroups of patients were performed using the usual 2 test or Fisher's exact test for categorical variables and Student's t test or Mann-Whitney test for continuous variables. Survival duration was calculated from diagnosis to date of death or censoring. Observed survival, specific (disease-related) survival, and relative survival rates were estimated in the entire study group and in different subgroups of patients according to location and histology of skin lesions. Observed survival and specific survival rates were estimated using the method of Kaplan and Meier.[20] For the estimation of observed survival, deaths were taken into account whatever the cause. For the specific survival analysis, only deaths from lymphoma were taken into account and patients who died from other causes were considered censored. For the relative survival analysis, a ratio between observed survival in the study population and expected survival according to general mortality was determined using tables of general mortality by age, sex, and period in every participating country.[21,22] Specific survival curves in different subgroups of patients were computed using the method of Kaplan and Meier.

Prognostic factors in the entire study group and in different subgroups of patients were evaluated by specific survival (disease-related) univariate and multivariate analyses using a Cox proportional hazards model.[23] Factors significant at the .2 level in univariate analysis were included in a stepwise regression multivariate analysis.

Results

Clinical Characteristics of the Total Group of 145 PCLBCL Patients

The clinical characteristics and follow-up data of the 145 patients included in the study are summarized in Table 2. The ratio of men to women was 1 (72:73). The age at diagnosis ranged between 23 and 92 years (mean, 64 years; median, 68 years). None had any history of noncutaneous lymphoma or leukemia. Fifteen patients (10%) had a history of cutaneous pseudolymphoma. Only one patient had been diagnosed as having a small-cell primary cutaneous B-cell lymphoma before it evolved into a large B-cell lymphoma. Clinically, patients presented with cutaneous nodules or tumors (94%) or deeply infiltrated plaques (6%). Therapy resulted in a complete remission in 131 (90%) of 145 patients. Thirty-five (24%) of 145 patients developed extracutaneous disease. The mean time until extracutaneous dissemination was 22 months. The extracutaneous progression was restricted to the lymph nodes in 12 cases, whereas 23 patients developed a visceral disease either associated with lymph node involvement (nine cases) or not (14 cases). Anatomic sites of visceral dissemination included the CNS (four cases), the bone marrow (four cases), the bones (four cases), the lung (three cases), the small intestine (two cases), the spleen (two cases), the testis (two cases), the kidney (two cases), the heart (two cases), the breast (one case), the thyroid (one case), and the brachial plexus (one case). Twenty-six (18%) of 145 patients died of lymphoma, whereas 13 patients (9%) died of unrelated disease. Death from lymphoma occurred in 19 of 26 patients within 3 years after diagnosis. Disease-related death was extremely rare in younger patients: no patient younger than 63 and only five patients younger than 70 at the time of diagnosis died of lymphoma. The overall and disease-specific 5-year survival rates were 72% and 81%, respectively.

Prognostic Factors in the Total Group of PCLBCL Patients

Univariate and multivariate analyses of disease-specific survival were performed on the total group of 145 patients to identify independent prognostic factors. Univariate analysis showed that the following variables were related to death from lymphoma: older age (> 75 years; $P < .0001$); short duration of skin lesions before diagnosis (< 10 months; $P = .0013$); location on the leg (PCLBCL-leg v PCFCCL, $P < .0001$); presence of more than one skin lesion at diagnosis ($P = .03$); disseminated skin lesions ($P = .036$); increased LDH level ($P = .05$); and round-cell morphology ($P < .0001$). Sex, diameter of the largest skin lesion and occurrence of spontaneous regression had no significant effect on death from lymphoma. When multivariate

analysis was performed, the round-cell morphology (P < .0001), location on the leg (P = .002), and presence of more than one skin lesion at diagnosis (P = .01) remained significant independent factors associated with a poor prognosis (TABLE 3). In view of these results, the main features at diagnosis and follow-up data were studied within the four subgroups of patients determined by location and morphology, as well as within the two major EORTC groups (TABLE 2). Kaplan and Meier disease-specific survival curves of these different subgroups of patients are shown in FIG. 2.

Comparison Between PCFCCL and PCLBCL-Leg

On the basis of the criteria of the EORTC classification,[6] 97 patients were assigned to the PCFCCL group and 48 patients were assigned to the PCLBCL-leg group according to site of presentation. In the PCFCCL group, the skin lesions were confined to the head and the neck (40 cases), a localized area on the trunk (45 cases), or the arm (one case), or they involved several anatomic sites excluding the leg (11 cases). The other clinical findings at diagnosis and follow-up data are listed in Table 2. In the PCFCCL group, 11 (11%) of 97 patients developed extracutaneous disease, six (6%) of 97 patients died of lymphoma, and the estimated overall and disease-specific 5-year survival rates were 85% and 94%, respectively.

In the PCLBCL-leg group, the skin lesions were confined to one leg (34 patients) or both legs (eight patients) in 42 of 48 patients. The other six patients had tumors on one or both legs associated with skin lesions at other sites. Follow-up data in this group indicate that 24 (50%) of 48 patients developed extracutaneous disease, and 20 (42%) of 48 died of lymphoma. The estimated overall and disease-specific 5-year survival rates were 42% and 52%, respectively.

A comparison between the two EORTC groups demonstrated that patients with PCLBCL-leg were older than patients with PCFCCLs (mean age, 73 v 60 years, P < .0001) and had more frequently disseminated skin lesions (P = .01), short duration of lesions before diagnosis (P < .0001), elevated LDH levels (P = .04), round-cell morphology (75% v 17.5%, P < .0001), and positive bcl-2 staining (P < .0001). Moreover, they were at increased risk of developing

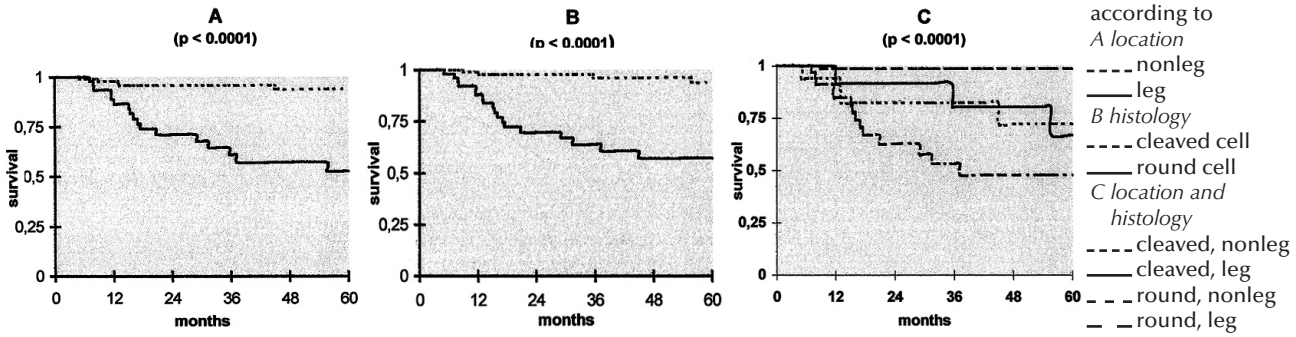

FIGURE 2. Kaplan-Meier–specific survival curves according to *A location* nonleg, leg; *B histology* cleaved cell, round cell; *C location and histology* cleaved, nonleg; cleaved, leg; round, nonleg; round, leg

Table 2. Main Findings at Diagnosis and Follow-Up Data in the Entire Study Group and According to Location and Histology

		PCFCCL			PCLBCL-Leg			
	All Patients	Total	Round	Cleaved	Total	Round	Cleaved	P*
No. of cases	145	97	17	80	48	36	12	
Age, years								< .0001
Mean	64	60	67	58	73	76	65	
Median	68	63	69	60	76	76	70.5	
Range	23-92	23-88	36-80	23-88	27-92	59-92	27-83	
Sex								.12
Male	72	52	9	43	20	15	5	
Female	73	45	8	37	28	21	7	
Duration before diagnosis								< .0001
< 10 months	76	40	8	32	36	31	5	
> 10 months	69	57	9	48	12	5	7	
No. of lesions								.17
1	47	36	5	31	11	10	1	
2-5	57	37	8	29	20	13	7	
> 5	41	24	4	20	17	13	4	
Largest skin lesion								.09
< 2 cm	12	11	2	9	1	0	1	
2-5 cm	86	57	9	48	29	21	8	
5-10 cm	33	18	1	17	15	12	3	
> 10 cm	14	11	5	6	3	3	0	
Extent								.01
Single	47	36	5	31	11	10	1	
Localized	73	50	11	39	23	16	7	
Disseminated	25	11	1	10	14	10	4	
bcl-2 expression								< .0001
Negative	35	33	2	31	2	1	1	
Positive	20	4	2	2	16	15	1	
Not done	90	60	13	47	30	20	10	
Initial therapy								.1
Radiotherapy	76	52	9	43	24	17	7	
Chemotherapy†	40	21	5	16	19	17	2	
Radiotherapy + chemotherapy†	11	8	0	8	3	1	2	
Excision	11	10	1	9	1	1	0	
None	7	6	2	4	1	0	1	
Complete response								.01
Yes	131	92	14	78	39	27	12	
No	14	5	3	2	9	9	0	
Relapse‡								< .0001
No	76	64	6	58	12	6	6	
Yes	55	28	8	20	27	21	6	
Extracutaneous progression								< .0001
No	110	86	10	76	24	18	6	
Yes	35	11	7	4	24	18	6	
Status								< .0001
Alive, disease free	93	78	8	70	15	10	5	
Alive with disease	13	6	2	4	7	5	2	
Died of lymphoma	26	6	5	1	20	17	3	
Died, other cause	13	7	2	5	6	4	2	
5-Year survival rate, %								
Overall	72	85	60	92	42	40	52	< .0001
Disease-specific	81	94	72	99	52	48	67	< .0001
Relative survival	84	96	71	100	57	55	64	< .0001

*Indicates differences between the PCFCCL group and the PCLBCL-leg group. For 5-year survival rates, *P* values were calculated from comparison of survival curves.

†Consisted of a multiagent chemotherapy in all cases but one.

‡Relapses were considered only in patients who achieved a complete response (131 cases).

extracutaneous disease (50% v 11%; P < .0001) and had a poorer 5-year disease-specific survival rate (52% v 94%; P < .0001) (TABLE 2 and FIG 2A).

Prognostic Parameters Within the PCFCCL and PCLBCL-Leg Groups

Statistical analysis for potential risk factors within these two EORTC groups demonstrated the following results. Within the PCFCCL group, multivariate analysis of disease-specific survival showed that only round-cell morphology (P = .0002)—but not age, duration of skin lesions before diagnosis, size, or number and extent of skin lesions—was significantly related to death from lymphoma. Five of six lymphoma-related deaths in this group occurred in patients with round-cell morphology.

Within the PCLBCL-leg group, multivariate analysis of disease-specific survival showed that multiple skin lesions at diagnosis (P = .001) and round-cell morphology (P = .003)—but not age, duration of skin lesions before diagnosis, or size and extent of skin lesions—were independent adverse prognostic factors. Further analysis of the relation between number and extent of skin lesions and survival showed that only one (9%) of 11 patients with a solitary tumor, compared with 12 (52%) of 23 patients with multiple tumors on one leg, and seven (50%) of 14 patients with generalized skin lesions including one or both legs died of lymphoma (P = .01).

Reproducibility Study

Among 38 cases studied for reproducibility, 21 cases (55%) were classified consistently as either round-cell or cleaved-cell PCLBCL by all of the six pathologists, in accordance with the result obtained by consensus during the histologic review. In seven cases (18%), all but one of the six pathologists agreed with the classification. In the remaining 10 cases (26%), two or more pathologists disagreed with the others and with the result of the histologic review. There was no significant difference between the Dutch and the French panels of pathologists for the rate of misclassification.

Table 3. Results From Multivariate Analysis in 145 Patients With PCLBCL

	RR	95% CI	P
Histology			< .0001
Cleaved	1		
Round	8.5	2.7-27	
Site/EORTC group			.002
Nonleg, PCFCCL	1		
Leg, PCLBCL-leg	4.2	1.5-11.5	
No. of lesions			.01
One	1		
Two or more	4.2	1.2-15	

Abbreviations: RR, relative risk; CI, confidence interval.

Discussion

Previous studies demonstrated that PCLBCL-leg differs from PCFCCL that arises at other sites by several characteristics, including age at presentation and bcl-2 protein expression, and by a more unfavorable prognosis.[5,6,8,11,12,24] For these reasons, PCLBCL-leg was included as a separate group in the EORTC classification.[6] However, delineation of this subgroup of PCLBCL patients on the basis of site has been much disputed.[13-17] Indeed, the respective role of site and other potential clinical or histologic prognostic factors had to be evaluated in a large multivariate study. Such multivariate analyses were rarely performed in primary cutaneous lymphomas. In a recent evaluation of 158 patients with a primary cutaneous lymphoma other than mycosis fungoides and the Sézary syndrome,[8] we found that the prognostic group according to the EORTC classification and the distribution of skin lesions were independent prognostic factors. However, this previous study included only a minority of patients with a PCLBCL and was unable to identify specific prognostic factors in these lymphomas which represent the most controversial group of the EORTC classification. In particular, the delineation of PCLBCL-leg as an independent subgroup had to be validated in a large international study restricted to PCLBCL.

In this European multicenter study of 145 patients with PCLBCL, we found that round-cell morphology, the location on the leg, and multiple skin lesions at diagnosis were independent adverse prognostic factors. Other characteristics, including age, had no significant effect on death from lymphoma after morphology, site, and number of skin lesions were taken into account.

This study shows that location is an independent prognostic factor in PCLBCL and provides further evidence that major differences exist between PCLBCL presenting on the leg and PCLBCL presenting at other sites. Patients from this latter group, included in the PCFCCL group in the EORTC classification for primary cutaneous lymphomas, presented with skin lesions on the head or trunk in most cases, rarely developed extracutaneous disease, and had an excellent prognosis with overall and disease-specific 5-year survival rates of 85% and 94%, respectively.

In contrast, patients with PCLBCL-leg were older, developed extracutaneous disease more often, and had a significantly poorer prognosis, with overall and disease-specific 5-year survival rates of 42% and 52%, respectively. In addition, the duration of skin lesions before diagnosis was much shorter in this group. In contrast to 14 (14%) of 97 patients with PCFCCL, only one (2%) of 48 patients with PCLBCL-leg had a history of a pseudo-B-cell lymphoma. Histologically, PCLBCL-leg much more frequently showed a predominance of round blasT-cells (75% v 17.5%; $P < .0001$) and much more often expressed bcl-2 protein

(TABLE 2). Expression of bcl-2 protein was not included in the multivariate prognostic analysis, since bcl-2–stained sections were only available in approximately 35% of cases. Therefore, additional studies are required to determine whether bcl-2 protein expression is primarily related to site or to a round-cell morphology and whether it represents an independent prognostic parameter in PCLBCL. In the present study, tumors were not investigated for the presence of the 14;18 translocation. However, a previous study demonstrated that the increased bcl-2 expression in PCLBCL-leg was not associated with the 14;18 translocation.[12]

The most discriminating prognostic parameter in the total group of 145 patients with PCLBCL was a predominance (> 50%) of large B-cells with round nuclei. Although there was an important overlap between location and morphology, this parameter remained an independent prognostic factor both in the PCFCCL group and the PCLBCL-leg group. This observation has not been reported previously. Therefore, the question arises of whether PCLBCL should be subdivided primarily on the basis of morphology rather than site, as suggested in the EORTC classification. However, histologic subclassification of diffuse large B-cell lymphomas in a reproducible way is notoriously difficult (Revised European-American Lymphoma classification).[18] Because of these difficulties, we preferred a simple subdivision on the basis of more or less than 50% blasT-cells with round nuclei. The reproducibility of this subdivision was evaluated in a small sample because it was not anticipated that multivariate analysis would indicate morphology as the most discriminating parameter. We found that

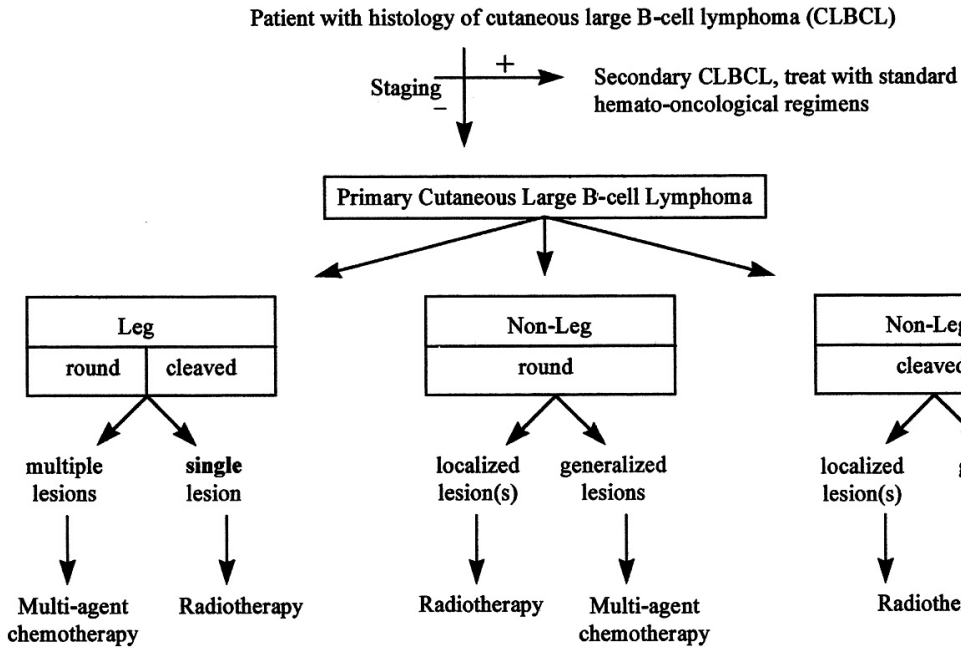

FIGURE 3. Recommended guidelines for managing the treatment of PCLBCLs. *In rare cases when radiotherapy is practically impossible (numerous or extremely thick lesions), multiagent chemotherapy can be administered.

28 (74%) of 38 cases were classified consistently as either round-cell or cleaved-cell PCLBCL by all or all but one of six pathologists. This demonstrates that distinction on the basis of morphology may be difficult in some cases and that a primary subdivision of PCLBCL on this basis would probably have a lower reproducibility than the more simple classification according to location (EORTC).[6] However, morphology constitutes an independent additional prognostic factor that should be taken into account for a more accurate management and treatment of PCLBCL (**Fig 3**).

The presence of multiple skin lesions at diagnosis was the last independent prognostic factor associated with death from lymphoma in the total group of 145 PCLBCL patients. This result has to be interpreted in view of prognostic analyses in subgroups before being translated into guidelines for practical management of PCLBCL. Within the PCFCCL group, only round-cell morphology was associated with a poor prognosis. Neither the number of skin lesions nor the presence of multifocal as opposed to solitary or localized skin lesions was significantly related to survival, which is consistent with the results of previous studies.[5,6,25] In contrast, both round-cell morphology and the presence of multiple skin lesions at diagnosis were significant adverse prognostic factors within the PCLBCL-leg group. Furthermore, the number of skin lesions was indeed the most important prognostic parameter in these patients. The 5-year survival rate was100% in patients with a single skin tumor on one leg versus 45% and 36% in patients with multiple tumors on one or both legs, respectively. Therefore, we suggest that only patients with a single tumor should be treated with radiotherapy. All other patients with PCLBCL-leg can probably best be treated with systemic chemotherapy.

In view of the results of this prognostic analysis in 145 patients with PCLBCL, practical guidelines for appropriate management and treatment can be provided (**Fig. 3**). Four subgroups can be distinguished. PCFCCL with a cleaved-cell morphology is the most common subgroup. The disease-related 5-year survival rate in this group was 99% (**Fig 2C**), and the 5-year relative survival rate was 100%. This indicates that mortality in these patients does not exceed mortality in a similar cohort matched by age and sex in the general population. Radiotherapy is the preferred mode of treatment in this group, probably even in patients presenting with multifocal skin lesions.[25] PCFCCLs with a round-cell morphology are uncommon and have a more unfavorable prognosis. Although definite conclusions cannot be drawn from this small group, we suggest that patients presenting with a single lesion or few clustered lesions can best be treated with radiotherapy, whereas in case of multifocal skin lesions, systemic chemotherapy is required. Most patients with PCLBCL-leg have a round-cell morphology. Cases of PCLBCL-leg with a cleaved-cell morphology are less common and have a somewhat better prognosis. However, irrespective of the histologic subtype, patients with PCLBCL-leg should be treated with systemic chemotherapy whenever possible.[6,8,11,26] Only in patients presenting with a single tumor may radiotherapy be preferred. However, no

definite conclusions can yet be drawn only on the basis of retrospective studies. Appropriate clinical trials are necessary to validate these therapeutic guidelines.

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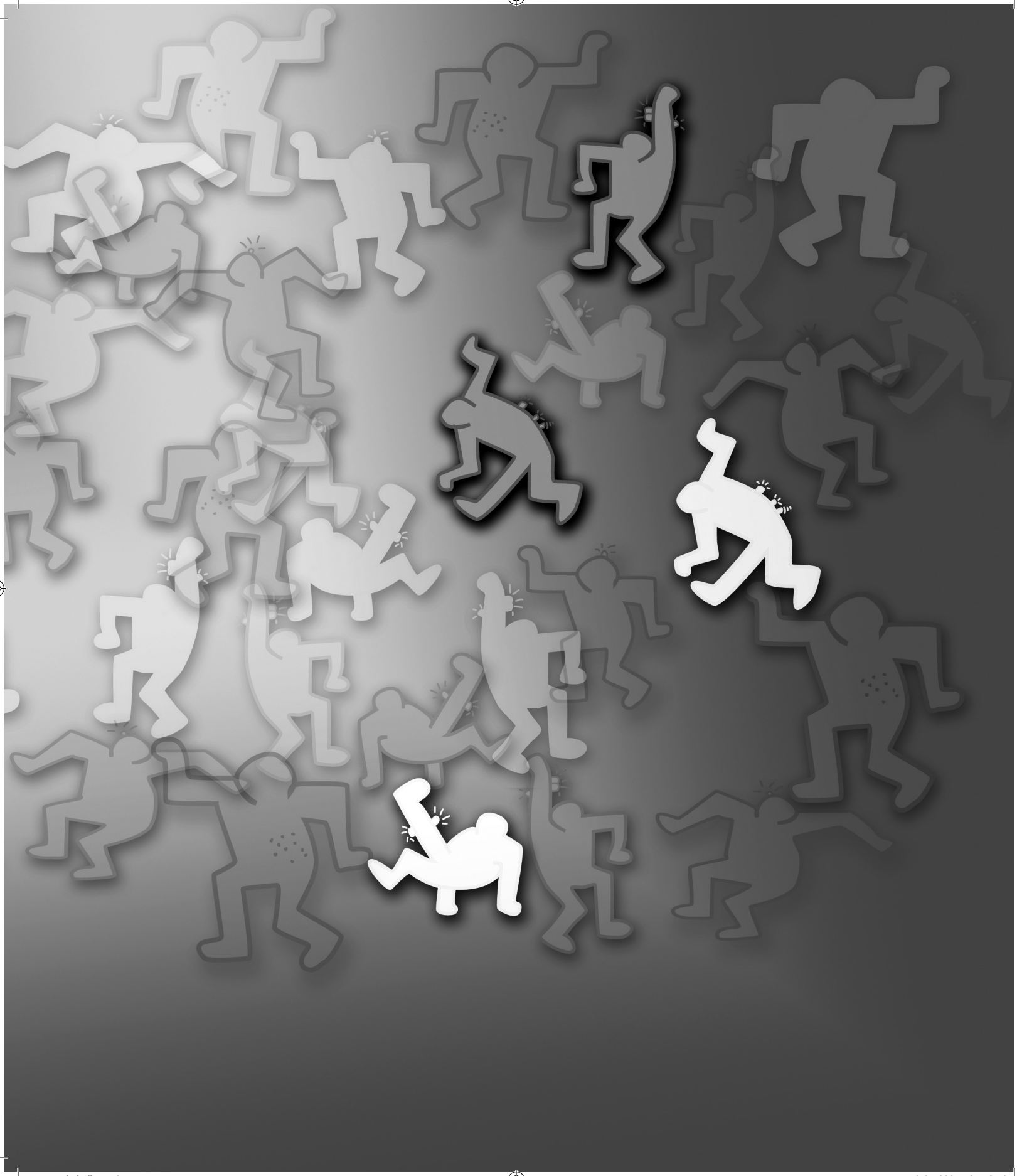

CHAPTER 7

Treatment of multifocal primary cutaneous B-cell lymphoma: a clinical follow-up study of 29 patients

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Marcel W. Bekkenk [1]
Maarten H. Vermeer [1]
Ed M. Noordijk [2]
Freerk Heule [3]
Pieter C. van Voorst Vader [4]
Willem A. van Vloten [5]
Marie-Louise Geerts [6]
Chris J.L.M. Meijer [7]
Rein Willemze [1]

1. Department of Dermatology, Free University Hospital, Amsterdam, the Netherlands
2. Department of Radiation Oncology, Leiden University Medical Center, Leiden, the Netherlands
3. Department of Dermatology, University of Rotterdam, Rotterdam, the Netherlands
4. Department of Dermatology, University of Groningen, Groningen, the Netherlands
5. Department of Dermatology, University of Utrecht, Utrecht, the Netherlands
6. Department of Dermatology, University of Ghent, Ghent, Belgium
7. Department of Pathology, Free University Hospital, Amsterdam, the Netherlands

Abstract

Purpose

Although patients with primary cutaneous B-cell lymphoma (CBCL) and localized skin lesions are generally treated with radiotherapy and have an excellent prognosis, the clinical behavior and optimal treatment of CBCL presenting with multifocal skin lesions are less well defined. In this study, we evaluated the clinical behavior of and results of treatment for multifocal CBCL in 29 patients, and we formulated therapeutic guidelines.

Patients and methods

The study group included 16 patients with primary cutaneous follicular center-cell lymphoma (PCFCCL), eight with primary cutaneous immunocytoma (PCI), and five with primary cutaneous large B-cell lymphoma presenting on the legs (PCLBCL of the leg).

Results

Only one of the 24 patients with multifocal PCFCCL or PCI developed extracutaneous disease, and no patient died from lymphoma (median follow-up, 54 months). In patients with PCFCCL, treatment with either multiagent chemotherapy (nine patients) or radiotherapy directed toward all skin lesions (five patients) proved equally effective in terms of complete remission, relapse, and survival. In contrast, all five patients with PCLBCL of the leg developed extracutaneous disease, and four of the five died from systemic lymphoma, 8 to 36 months (median, 21 months) after diagnosis.

Conclusion

The results of these preliminary studies suggest that patients with PCFCCL or PCI presenting with multifocal skin lesions have the same excellent prognosis that patients with localized PCFCCL or PCI have and that radiotherapy directed toward all skin lesions is as effective as multiagent chemotherapy. Patients with PCLBCL of the leg have a more unfavorable prognosis, particularly patients presenting with multifocal skin lesions. This last group should always be treated with multiagent chemotherapy.

Introduction

Primary cutaneous B-cell lymphomas (CBCLs) constitute approximately 20% to 25% of all cutaneous lymphomas.[1,2] The European Organization for Research and Treatment of Cancer (EORTC) divides primary CBCLs into primary cutaneous follicular center-cell lymphoma (PCFCCL), primary cutaneous immunocytoma (PCI), and primary cutaneous large B-cell lymphoma (PCLBCL) of the leg.[2] PCFCCLs, which comprise malignant B-cell lymphomas classified as centroblastic/centrocytic or centroblastic lymphoma in the updated Kiel classification,[3] represent the most common type of CBCL. These lymphomas generally

present with localized skin lesions (usually localized on the head or trunk), rarely disseminate to extracutaneous sites, and are associated with an excellent prognosis, with a 5-year survival rate of more than 95%.[4-7] PCI more often presents with skin lesions on the arms and legs and is also associated with an excellent prognosis.[8,9] Disease-related deaths have not been reported thus far. In the Revised European-American Lymphoma classification,[10] similar lymphomas are designated primary cutaneous marginal zone B-cell lymphomas or mucosa-associated lymphoid tissue–type lymphomas.[11-13] PCLBCLs of the leg, which histologically resemble centroblastic lymphomas in most cases and immunoblastic lymphomas less commonly, have recently been delineated as a separate group. This type of CBCL predominantly affects elderly patients, more often disseminates to extracutaneous sites, and is associated with a more unfavorable prognosis (5-year survival rate, 58%) compared with the other two groups.[14]

In patients with CBCL presenting with solitary or localized skin lesions, radiotherapy is the preferred treatment.[15,16] However, the optimal treatment for patients presenting with multifocal skin lesions, which is more uncommon, has not yet been well defined. Because patients with such lymphomas are considered to have a higher risk for developing extracutaneous disease, some studies suggest that these patients should be treated with aggressive multiagent chemotherapy.[17] In the present study, we evaluated the clinical and histologic data from 29 patients with primary CBCL and multifocal skin lesions who registered with the Dutch Cutaneous Lymphoma Group between 1985 and 1997. The main goals of this study were, first, to determine whether the clinical behavior of multifocal CBCL differs from that of the more common localized CBCL and, second, to formulate guidelines for the management and treatment of patients with multifocal CBCL.

Patients and methods

All patients with primary CBCL with multifocal skin lesions at presentation who were registered with the Dutch Cutaneous Lymphoma Group were selected for this study. Multifocal skin disease was defined as skin involvement of at least two nonadjacent skin areas. Patients presenting with multiple skin lesions that did not fit into one radiation field were considered to have multifocal skin disease. Of the 149 patients with primary CBCL registered between 1985 and 1997, 29 (14%) had multifocal lesions at the time of diagnosis, a proportion similar to those in other large series.[7,18] In all cases, adequate staging procedures—including physical examination, complete blood cell counts, hepatic and renal function tests, chest radiography, abdominal computed tomography, and bone marrow cytology and histology—had been performed and extracutaneous disease had not been demonstrated. According to the EORTC classification for primary cutaneous lymphomas, this study group included 16 patients with PCFCCL (patients no. 1 through 16), eight with PCI (patients no. 17 through 24), and five with PCLBCL of the leg (patients no. 25 through 29) (**Table 1**). This latter group included

patients presenting with skin lesions on both lower legs, and three of these patients had skin lesions at other sites as well. Follow-up data had been collected each year from referring dermatologists or oncologists and were available for all cases in the registry of the Dutch Cutaneous Lymphoma Group.

Results

The main clinical characteristics of the three patient groups are presented in Tables 1 and 2. The total group of 29 patients included 17 men and 12 women. The median age at the time of diagnosis was 56 years (range, 26 to 92 years). The length of time before diagnosis that patients had had skin lesions varied between 2 and 480 months (median, 24 months). In eight of the 29 patients, a diagnosis of pseudo–B-cell lymphoma had been made on viewing the same lesions (patient no. 17) or other lesions (patients no. 9, 10, 16, 20, 22, 23, and 24) 24 to 192 months (median, 60 months) before a definite diagnosis of CBCL was made.

The group of patients with PCFCCL was composed of 16 patients, 11 men and five women. The median age at the time of diagnosis was 56 years (range, 27 to 84 years). Clinically, these multifocal PCFCCLs usually involved the trunk (Fig 1). These 16 patients presented with multiple tumors, nodules, and/or plaques on the back (n = 16), the chest or abdomen (n = 10), the arms (n = 7), and/or the head and neck region (n = 2). Initial therapy consisted of six cycles of multiagent chemotherapy—including courses of cyclophosphamide, doxorubicin, vincristine, and prednisone (CHOP) therapy (in eight patients: patients no. 6 through 13) and courses of cyclophosphamide, vincristine, and prednisone therapy (patient no. 14)—or radiotherapy directed toward all visible skin lesions (in five patients: patients no. 1 through 5) (Table 1). Radiotherapy consisted of electron beam irradiation (4 to 10 million electron volts) with a radiation dose of 40 Gy. Of the two remaining patients, one patient (patient no. 15) refused any aggressive treatment and was therefore treated with topical corticosteroids only, and the other patient (patient no. 16) did not receive any treatment, because the skin lesions showed the tendency to regress spontaneously.

Initial treatment in the PCFCCL group resulted in complete remission in 15 of 16 patients, including patient no. 16, all of whose skin lesions disappeared without any therapy. The disease-free survival time for these 15 patients varied between 11 and 72 months (median, 38 months). Cutaneous relapse was noted in four of 16 patients (patients no. 11, 14, 15, and 16). Only one patient (patient no. 12) developed positive cervical lymph nodes, but these lesions regressed spontaneously and the patient did not require additional treatment. It is interesting to note that cutaneous or extracutaneous relapse occurred in three of the nine patients treated with multiagent chemotherapy but in none of the five patients in whom all initial skin lesions had been treated with radiotherapy. Follow-up data indicated that none of

Table 1. Clinical Characteristics of 29 Patients With Multifocal Primary CBCL

Patient No.	Sex/Age (years)	Clinical Presentation	Therapy	Result	Relapse	Therapy	Status/Follow-Up (months)
PCFCCL							
1	M/34	Large area of tumors and plaques on back and on side of abdomen	RT	CR	No		A^0/73
2	M/64	Plaques on back and abdomen	RT	CR	No		A^0/74
3	M/27	Plaques and nodi on back and on right upper arm	RT	CR	No		A^0/41
4	F/27	Nodi on lower back, abdomen, and both arms	RT	CR	No		A^0/35
5	M/70	Large area of plaques, papules, and nodules on back, neck, and chest	RT	CR	No		D^0/55
6	M/68	Tumors, nodules, and plaques on abdomen and right side of back	CHOP	CR	No		D^0/42
7	M/56	Nodi on arms and left shoulder	CHOP	CR	No		A^0/45
8	M/58	Plaques on right elbow and left scapula	CHOP	CR	No		A^0/32
9	F/45	Tumors and nodi on breast, left arm, and back	CHOP	CR	No		A^0/59
10	M/36	Nodi on chest and lower and upper back	CHOP	CR	No		A^0/58
11	M/56	Plaques on face and trunk	CHOP	CR	Skin	Surgery and RT	A^0/53
12	F/60	Nodi on back, pubic area, left arm, and abdomen	CHOP	CR	EC	Wait and see	A^0/50
13	M/49	Nodi on upper arm, back, and nates	CHOP	CR	No		A^0/20
14	M/69	Tumors and plaques on abdomen and back	COP	CR	Skin	RT	A^0/179
15	F/84	Tumors on head and back	Topical corticosteroids	PR	Skin	Topical corticosteroids	D^0/75
16	F/64	Plaques and nodi on back, abdomen, and chest	None	CR	Skin	Wait and see	A^+/49
PCI							
17	F/53	Nodi on back, shoulders, nates, and both legs	CHOP	CR	Skin	RT and etopside	A^+/60
18	F/38	Plaques and nodi on both arms	pRT	PR	Skin	RT	A^+/39
19	M/56	Tumors and plaques on arms and left leg	pRT	PR	Skin	RT	A^0/81
20	M/28	Plaques on both legs	Partial surgery	PR	Skin	Topical corticosteroids	A^+/61
21	M/80	Tumors and nodi on head and back	COP	PR	Skin	RT	D^0/18
22	M/26	Tumors and nodi on both arms, both legs, and back	Chlorambucil	PR	Skin	Wait and see	A^+/149
23	M/45	Plaques on both legs and abdomen	Topical corticosteroids	PR	Skin	RT	A^+/14
24	F/42	Tumors and plaques on right shoulder and arms	Topical corticosteroids	PR	Skin	RT and Topical corticosteroids	A^+/95
PCLBCL of the leg							
25	F/84	Tumors on lower legs	RT	CR	EC	None	D^+/8
26	F/70	Nodi and plaques on lower legs	COP	CR	Skin and EC	CNOP	D^+/36
27	F/76	Large tumors right leg and flank	COP and RT	PR	Skin and EC	None	D^+/11
28	M/35	Plaques and tumors on legs, arms, and pubic region	CEOP	PR	Skin and EC	BMT	A^0/85
29	F/92	Plaques and nodi on thighs, lower legs, forehead, and back	Etopside	PR	Skin and EC	CHOP	D^+/31

Abbreviations: A^0, alive without disease; A^+, alive with disease; BMT, bone marrow transplantation; CEOP, cyclophosphamide, etoposide, vincristine, prednisone; CHOP, cyclophosphamide, doxorubicin, vincristine, predisone; COP, cyclophosphamide, vincristine, prednisone; CR, complete remission; D^0, died from unrelated disease; D^+, died from lymphoma; EC, extracutaneous; PR, partial remission; pRT, radiotherapy directed toward some lesions; RT, radiotherapy.

these 16 patients died from lymphoma, after a median follow-up of 52 months (range, 20 to 179 months).

The group of patients with PCI consisted of five men and three women. The median age at the time of diagnosis was 43 years (range, 26 to 80 years). Consistent with findings of previous studies, these lymphomas usually involved the arms and/or legs (seven of eight cases), whereas the head and trunk were involved in one and four cases, respectively. Initial treatment was more varied than that in the PCFCCL group and consisted of multiagent chemotherapy (patients no. 17 and 21), single-agent chemotherapy (patient no. 22), radiotherapy or surgical excision of only some of the skin lesions (patients no. 18, 19, and 20), or treatment with topical corticosteroids (patients no. 23 and 24) (Table 1). Only the patient who was treated with CHOP therapy achieved complete remission. Cutaneous relapse occurred in all eight patients, including the patient treated with CHOP therapy. However, none of these eight patients developed extracutaneous disease or died from lymphoma, after a median follow-up of 65 months (range, 14 to 149 months). Partial spontaneous regression occurred in 50% of cases; complete spontaneous regression of all lesions did not occur.

Table 2. Summary of Clinical Characteristics of 29 Patients With Multifocal Primary CBCL

	Total (n = 29)	PCFCCL (n = 16)	PCI (n = 8)	PCLBCL of the Leg (n = 5)
Sex (M:F)	17:12	11:5	5:3	1:4
Age, years				
Median	56	56	43	76
Range	26-92	27-84	26-80	35-92
Duration of skin lesions before diagnosis, months				
Median	24	31	54	4.5
Range	2-480	2-480	3-192	3-228
History of pseudolymphoma	8	3	5	0
Localization				
Trunk	23	16	4	3
Extremities	19	7	7	5
Head/neck	4	2	1	1
Therapy				
Multiagent chemotherapy	14	9	2	3
Single-agent chemotherapy	2	0	1	1
Radiotherapy	8	5	2*	1
Surgery	1	0	1*	0
Topical corticosteroids	3	1	2	0
None	1	1	0	0
Result				
Complete remission	18	15†	1	2
Partial remission	11	1	7	3
No response	0	0	0	0
Spontaneous remission				
Complete	1	1	0	0
Partial	8	3	4	1
Relapse				
Cutaneous	16	4	8	4
Extracutaneous	6	1	0	5
Status				
Alive without disease	14	12	1	1
Alive with disease	7	1	6	0
Died from unrelated disease	4	3	1	0
Died from lymphoma	4	0	0	4
Length of follow-up, months				
Median	50	52	65	31
Range	8-179	20-179	14-149	8-85
5-year survival rate, %	88	100	100	20

*Some of the skin lesions.
†Including one spontaneous complete remission.

The group of patients with PCLBCL of the leg included four women and one man. The median age at diagnosis was 76 years (range, 35 to 92 years). Clinically, these patients presented with plaques and tumors on both lower legs (patients no. 25 and 26) or on the leg

or legs and other sites as well (Fig 2). Initial therapy, which was often suboptimal because of the age and general condition of the patients, consisted of single-agent or multiagent chemotherapy (patients no. 26 through 29) or radiotherapy directed toward all skin lesions (patient no. 25).

Only two patients with PCLBCL of the leg achieved complete remission, which was, however, short-lived (6 and 7 months). All five patients developed extracutaneous disease, 7 to 36 months (median, 18 months) after diagnosis. Two patients (patients no. 25 and 27) died rapidly, before further treatment could be initiated. In two patients (patients no. 26 and 29), treatment with more aggressive chemotherapy (CHOP or CHOP-like therapy) resulted in only partial remission. One patient (patient no. 28), a 35-year-old man who only partially responded to cyclophosphamide, etoposide, and vincristine therapy, received an autologous bone marrow transplant, which resulted in sustained complete remission. Follow-up data indicated that four (80%) of the five patients in this group died from systemic lymphoma, 8 to 36 months after diagnosis; only one patient remained alive and well. The median survival time for this group was 31 months (range, 8 to 85 months).

Discussion

Although there is general consensus among cutaneous lymphoma centers that primary CBCL presenting with solitary or localized skin lesions, irrespective of clinical or histologic subtype, should be treated with optimal doses of radiotherapy (40 Gy), the optimal treatment for the rare CBCL presenting with skin lesions at multiple sites has not been well defined. Some anecdotal reports suggest that patients with multifocal CBCL have a more unfavorable prognosis and should therefore be treated with aggressive multiagent chemotherapy.[17] The guidelines of the Dutch Cutaneous Lymphoma Group, most recently revised in 1990, also indicate that patients with PCFCCL and PCLBCL of the leg presenting with multifocal skin lesions are best treated with systemic chemotherapy. Patients with multifocal PCI are treated less aggressively because they rarely develop extracutaneous disease, and lymphoma-related deaths in this group have not yet been reported.[8,9]

These therapeutic guidelines, however, are mainly based on clinical experience and are not supported by published studies. In fact, follow-up data from large groups of patients with multifocal CBCL have never been published. In recent years, in view of the favorable prognosis for most patients with CBCL, there has been increasing reluctance to treat these patients with multifocal CBCL with multiagent chemotherapy, particularly when they present with only two or three skin lesions at different sites. In such patients, radiotherapy directed toward all visible skin lesions is considered an attractive alternative. In an attempt to create new guidelines for the treatment of patients with multifocal CBCL, we first evaluated clinical,

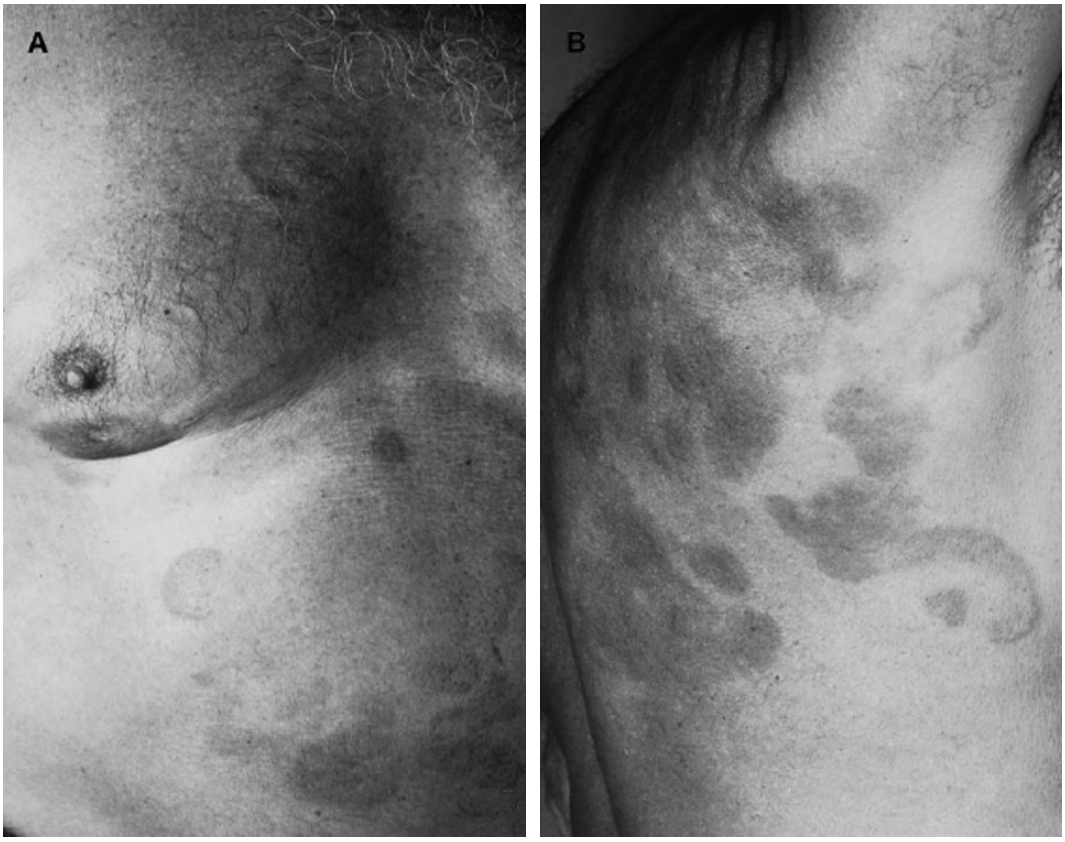

Figure 1. PCFCCL. Note the many plaques and nodules on the chest, abdomen, and back.

histologic, and follow-up data from 29 patients with multifocal CBCL who were registered with the Dutch Cutaneous Lymphoma Group between 1985 and 1997. We first wanted to determine whether the clinical behavior of multifocal primary CBCL differs from that of CBCL presenting with localized skin lesions.

Only six of the 29 patients in our study developed extracutaneous disease, and only four died from systemic lymphoma. However, analysis of the data for the separate groups of CBCL recognized in the EORTC classification for primary cutaneous lymphomas showed that only one of the 24 patients with PCFCCL or PCI developed extracutaneous disease and that none of these patients died from lymphoma, after a median follow-up of 54 months (range, 14 to 179 months). These data clearly indicate that patients with multifocal PCFCCL and those with multifocal PCI have the same low tendency to develop extracutaneous disease, and the same excellent prognosis, as do patients with the more common CBCLs presenting with localized skin lesions. Similar results can be found in the report of a study by Santucci et al,[7] in which 11 of 83 patients presented with multifocal skin lesions. In contrast, in our group

of patients with PCLBCL of the leg, all five patients developed extracutaneous disease, and four of the patients died from systemic lymphoma. These findings confirm the results of recent studies indicating that PCLBCLs of the leg represent a separate group, with a higher tendency to disseminate to extracutaneous sites and associated with a more unfavorable prognosis.[14,19] Most recently, it was found that PCLBCLs of the leg consistently express bcl-2 protein as well as Fas (CD95) ligand, whereas expression of Fas (CD95) is variable.[20,21] In contrast, PCFCCLs do not or rarely express bcl-2 protein and Fas ligand, whereas Fas is always strongly expressed. The differing expression of these apoptosis-related molecules may explain, at least in part, the different clinical behavior of these two types of primary CBCL.

Compared with our previous study of PCLBCL of the leg (18 patients),[14] in the present study the rates of extracutaneous relapse (38% v 100%) and lymphoma-related death (28% v 80%) were considerably higher. This increase may be related to the small sample size in the current study. However, recent evaluation of 21 patients with PCLBCL of the leg who were registered with the Dutch Cutaneous Lymphoma Group, including the 18 patients described previously,[14] shows that only one of six patients presenting with a single tumor on one leg died from lymphoma, after a median follow-up of 40 months (range, 18 to 120 months) (unpublished data). It is therefore possible that in this particular group, patients presenting with multifocal skin lesions (eg, skin lesions on both legs) have a worse prognosis than do

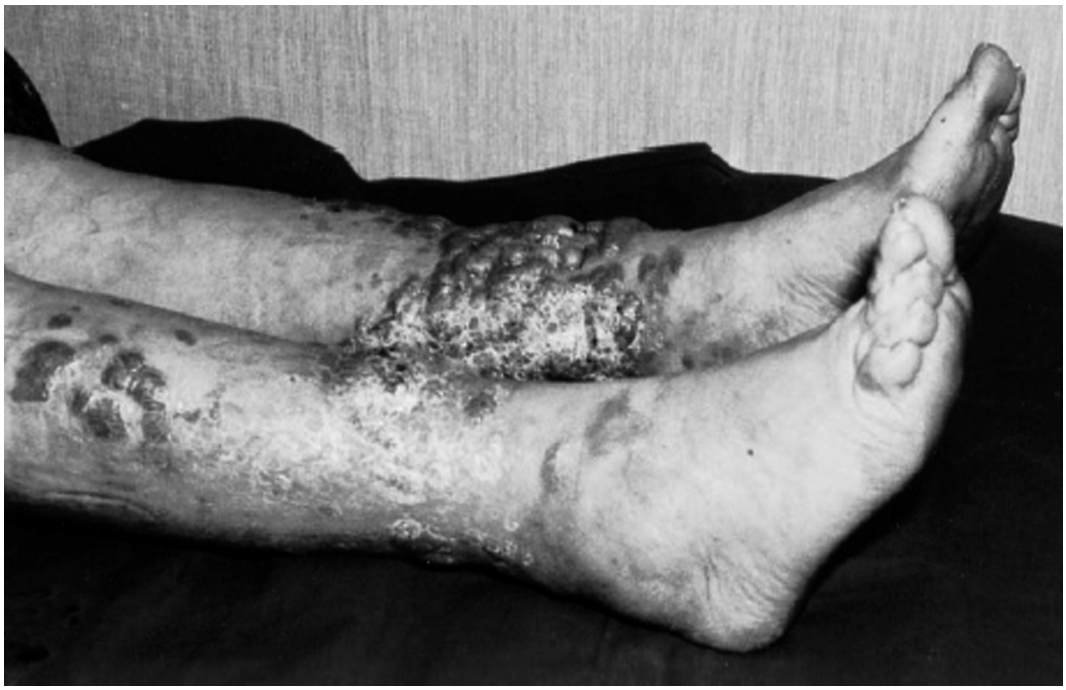

Figure 2. PCLBCL of the leg. Note the many tumors (some confluent) on both lower legs.

patients presenting with a skin lesion or lesions limited to one leg. A European multicenter study of more than 150 primary cutaneous large B-cell lymphomas has recently been started and will address this issue.

The ultimate goal of the present study was to create new guidelines for the treatment of patients with multifocal CBCL. The central issue to be addressed was which patients should be treated with aggressive multiagent chemotherapy (CHOP or CHOP-like therapy). The guidelines of the Dutch Cutaneous Lymphoma Group, formulated in 1990, indicated that all patients with multifocal CBCL, except for patients with PCI, should be treated with CHOP or CHOP-like therapy. However, the results of the present study indicate that in patients with multifocal PCFCCL, irradiation of all visible sites may be equally effective. Such an approach was taken in five patients (patients no. 1 through 5) and resulted in sustained complete remission, with a median disease-free survival time of almost 5 years. Relapse was not noted in these patients. In contrast, two of eight patients with multifocal PCFCCL treated with CHOP therapy had multiple cutaneous relapses (patient no. 11) or an extracutaneous relapse (patient no. 12). The other patients treated with CHOP achieved sustained complete remission, varying in length between 20 and 59 months. No major differences were found between the patients treated with radiotherapy and those treated with CHOP in terms of histologic subtype (centrocytic/centroblastic or centroblastic lymphoma), the number of affected skin sites, or total tumor burden. Taken together, these preliminary findings suggest that in patients with multifocal PCFCCL, irrespective of histologic appearance, radiotherapy directed toward all skin lesions is an effective and safe alternative. Only in exceptional cases—

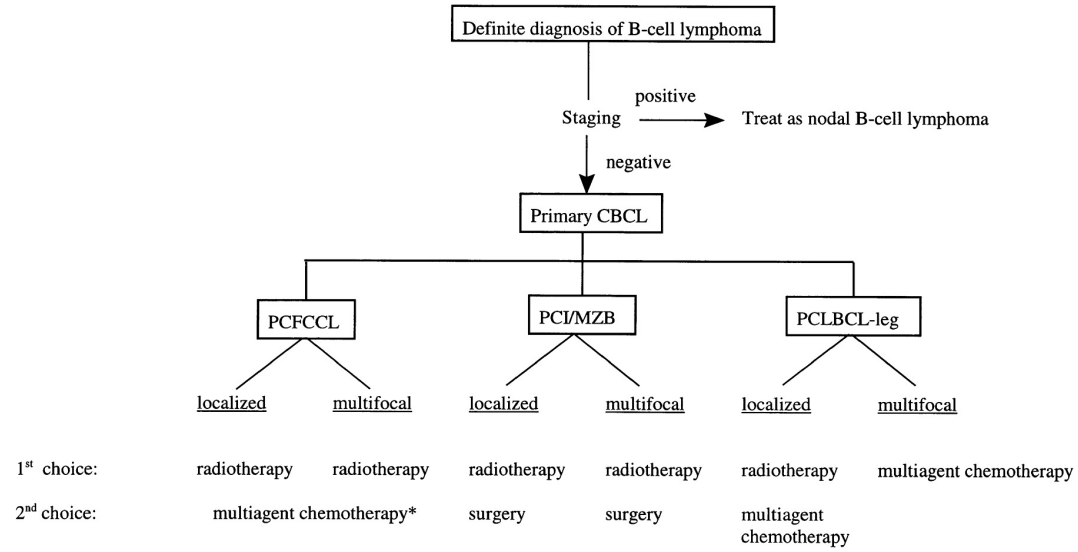

FIGURE 3. Dutch Cutaneous Lymphoma Group guidelines for the treatment of CBCL. In cases of Borrelia burgdorferi infection, antibiotic therapy should be tried first. *Use when radiotherapy is nearly impossible (when there are numerous or extremely thick lesions). MZB, marginal zone B-cell lymphoma.

involving numerous or extremely thick tumors—should CHOP therapy still be considered. In cases of cutaneous relapse with only one or a few skin lesions, radiotherapy is again the preferred treatment.

The prolonged complete remissions (up to 6 years or more) achieved in these patients with multifocal PCFCCL after irradiation of all visible skin lesions are intriguing. In particular, in such multifocal cases, one would expect low levels of circulating clonal B-cells and—given that these cells are unlikely to be affected by radiotherapy—recurring disease. However, the presence of circulating clonal B-cells in patients with CBCL has not been investigated thus far. These prolonged remissions are reminiscent of the results of total-skin electron beam irradiation in patients with early (patch/plaque)-stage mycosis fungoides (MF), namely 5-year relapse-free survival rates of 25% to 50%, depending on the extent of skin involvement.[22,23] Muche et al[24] demonstrated circulating clonal T-cells in more than 50% of patients with early MF but considered a relationship between the presence of circulating clonal T-cells and poor prognosis unlikely. Nevertheless, studies on the relationship between the presence of circulating clonal T-cells (in MF) or clonal B-cells (in CBCL) and disease-free survival would be of interest because they may provide a rationale for the optimal treatment in these conditions.

PCIs show the characteristic clinical behavior of low-grade malignant (small-cell) B-cell lymphomas.[25] Spontaneous regression of (part of the) skin lesions is frequently noted, and prognosis is excellent, as it is in patients with multifocal skin lesions. In addition, most patients have recurrent or persistent disease, and sustained complete remission or cure is rarely achieved. Therefore, these multifocal PCIs are best treated with radiotherapy or excision of individual skin lesions. When excision or radiation is no longer an option, because patients have too many lesions, nonaggressive chemotherapy—such as chlorambucil and/or prednisone therapy or perhaps even courses of cyclophosphamide, vincristine, and prednisone therapy—may be considered. Intralesional administration of recombinant interferon alfa has been suggested as an effective alternative in the treatment of both PCI and PCFCCL and could be a useful addition to the nonaggressive therapeutic options for these lymphomas, but the number of patients so treated who have reported on thus far is still small.[26-28] Moreover, the advantage of interferon alfa over radiotherapy is uncertain and further study is needed. In cases of small recurrent skin lesions, topical or intralesional administration of corticosteroids may be considered. Borrelia burgdorferi infections have been implicated in the pathogenesis of both pseudo–B-cell lymphomas and CBCLs, including PCI and PCFCCL.[29,30] In patients with serologic, bacteriologic, or molecular evidence of B. burgdorferi infection, treatment with antibiotics may result in complete remission and should therefore be attempted first.[29,30]

In accordance with previous findings by our group,[14] patients with PCLBCL of the leg with or without involvement of other cutaneous sites have a more unfavorable prognosis. In this type of CBCL, multifocal skin lesions (eg, on both lower legs) might be an additional risk factor. With the exception of patients presenting with one solitary tumor, patients with PCLBCL of the leg should be treated with CHOP or CHOP-like therapy whenever possible. Less aggressive therapies, sometimes necessary because of the age of these patients, are unlikely to result in sustained complete remission.

Finally, the results of the present study are also important for patients suspected of having CBCL and in whom a definite diagnosis cannot or cannot yet be made. The clinical consequences of not making a final diagnosis are generally minor, particularly in patients presenting with a solitary lesion. In such cases, radiotherapy or surgical excision may be a simple solution. However, in rare cases of suspected but not definite CBCL presenting with multifocal skin lesions, it is often difficult to decide whether aggressive chemotherapy should be given. The results of the present study clearly indicate that in such patients a conservative approach may be taken. This recommendation is supported by follow-up data from 14 patients with suspected CBCL, which is considered a separate type in the Dutch registry. Treatment for these patients consisted of topical and/or intralesional administration of corticosteroids, low-dose radiotherapy, or excision. In none of the patients was there progression to genuine CBCL, after a median follow-up of 36 months.

In conclusion, the results of this and other studies suggest that not only in CBCL patients with solitary or localized skin lesions but also in CBCL patients presenting with skin lesions at multiple sites, irradiation of all visible skin lesions is equally effective and may be preferable because of less systemic toxicity (Fig 3). Only in patients with PCLBCL of the leg (with the exception of those presenting with one solitary tumor) and patients with PCFCCL and numerous or extremely thick skin lesions is CHOP or CHOP-like therapy indicated. However, it must be noted that although this study, compared with other studies to date, involves by far the largest group of patients with multifocal primary CBCL, these guidelines are based on findings for relatively small groups of patients and therefore require additional confirmation.

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CHAPTER 8

Frequency of central nervous system involvement in primary cutaneous B-cell lymphoma

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Marcel W. Bekkenk [1]
Tjeerd J. Postma [3]
Chris J. L. M. Meijer [2]
Rein Willemze [4]

1. Department of Dermatology of the Free University Hospital, Amsterdam, the Netherlands
2. Department of Pathology of the Free University Hospital, Amsterdam, the Netherlands
3. Department of Neurology of the Free University Hospital, Amsterdam, the Netherlands
4. Department of Dermatology, Leiden University Medical Center, Leiden, the Netherlands

Abstract

Background

Primary cutaneous B-cell lymphoma (CBCL) constitutes 20% of all primary cutaneous lymphomas. Apart from primary cutaneous large B-cell lymphoma presenting on the legs (PCLBCL-leg), primary CBCLs run an indolent clinical course, rarely disseminate to extracutaneous sites, and have an excellent prognosis. Because of recent observations in two patients who developed central nervous system (CNS) involvement, follow-up data of all primary CBCL patients registered at the Dutch Cutaneous Lymphoma Group between 1985 and 1998 were investigated for evidence of CNS involvement.

Methods

Follow-up data from 160 primary CBCLs were evaluated. This group included 122 primary cutaneous follicle center cell lymphomas (PCFCCLs), 16 primary cutaneous immunocytomas or marginal zone B-cell lymphomas, and 22 PCLBCL-leg.

Results

Of all 160 patients with primary CBCLs, 11 died of lymphoma, including 4 of 122 patients (3%) with PCFCCL and 7 of 22 patients (32%) with PCLBCL-leg. Four of these 11 patients, including 3 with PCFCCL and 1 with PCLBCL-leg, had developed CNS involvement 3-93 months (median, 30 months) after diagnosis. All patients died 1-9 months (median, 7 months) after the development of CNS involvement. In the group of 122 patients with PCFCCL, CNS involvement occurred in 3 of 7 patients (43%) who developed extracutaneous disease and accounted for 3 of 4 lymphoma-related deaths (75%).

Conclusions

The results of this study indicate that approximately 2% of all primary CBCLs may develop CNS involvement. Whereas, in rare PCFCCL patients, developing extracutaneous disease CNS involvement was an important cause of death, patients with PCLBCL-leg and secondary CBCL died more frequently due to involvement of non-CNS organ systems.

Introduction

Cutaneous B-cell lymphomas (CBCLs) are a rare group of malignant B-cell lymphomas that present in the skin without evidence of extracutaneous involvement at the time of diagnosis. The recently proposed European Organization for Research and Treatment of Cancer (EORTC) classification[1] recognizes three different types of CBCL: primary cutaneous follicle center cell lymphoma (PCFCCL), primary cutaneous immunocytoma or marginal zone B-cell lymphoma, and primary cutaneous large B-cell lymphoma of the leg (PCLBCL-leg). Primary cutaneous plasmacytoma and primary cutaneous intravascular B-cell lymphoma are

extremely rare and have been included as provisional entities in the EORTC classification. Both PCFCCL and primary cutaneous immunocytomas are known for their indolent clinical behavior, their extremely low tendency to disseminate to extracutaneous sites, and their excellent prognosis (5-year survival rage > 95%).[2-6] Radiotherapy is the preferred mode of treatment not only for patients with solitary or localized skin lesions (±85% of patients) but probably also for patients with multifocal skin lesions.[7-9] PCLBCL-leg predominantly affects elderly patients, and these patients develop extracutaneous disease more often and have an intermediate prognosis (5-year-survival rate, 58%).[10,11]

The EORTC classification is clinically validated by long term follow-up data from a large group of primary cutaneous lymphomas registered at the Dutch Cutaneous Lymphoma Group.[1] Recently, the French Cutaneous Lymphoma Group confirmed the prognostic value of this classification.[12] From all of the patients in our registry, follow-up data are collected yearly. Recently, follow-up information was provided on two patients with primary CBCL who had developed involvement of the central nervous system (CNS), which proved fatal within several months.

CNS involvement has been reported regularly in patients with advanced stages of mycosis fungoides[13-18] and is common in patients with intravascular lymphoma.[19,20] However, detailed reports on CNS involvement in patients with a primary CBCL have not been published.

Because of these observations, the follow-up data from 168 primary CBCL patients registered at the Dutch Cutaneous Lymphoma Group were evaluated for evidence of CNS involvement. The results of this study, which revealed four primary CBCL patients with ultimate CNS involvement, are presented.

Materials and methods

From October 1985 to September 1998, 168 patients with primary CBCL were included in the registry of the Dutch Cutaneous Lymphoma Group. This group was comprised of 122 patients with PCFCCL, 16 patients with primary cutaneous immunocytoma, 22 patients with PCLBCL-leg, and a miscellaneous group of 8 patients with CBCL, including 4 patients with primary cutaneous intravascular large B-cell lymphoma who are not discussed further in this report. The diagnosis was based on a combination of histologic, immunophenotypic, and clinical criteria that have been described previously.[1] Briefly, PCFCCL is defined as CBCL composed of variable proportions of centrocytes (small or large, cleaved follicle center cells) and centroblasts (large, noncleaved follicle center cells), which are classified as either centroblastic-centrocytic or centroblastic in the updated Kiel classification.[21] In the majority of these patients, PCFCCLs are diffuse large cell lymphomas. Most patients (> 80%) with

PCFCCL have localized skin lesions either on the head or on the trunk at presentation. Patients with diffuse large cell lymphomas presenting with skin lesions on the leg(s) are considered as a separate group in the EORTC classification. Primary cutaneous immunocytoma or marginal zone B-cell lymphoma are defined by the presence of a proliferation of small lymphocytes, lymphoplasmacytoid cells, and plasma cells. In all 160 patients, adequate staging procedures (physical examination, complete blood cell counts, hepatic and renal function tests, chest radiography, abdominal computed tomography (CT), and bone marrow histology and cytology) at the time of diagnosis had failed to demonstrate extracutaneous disease.

For the purpose of comparison, 40 patients who were included in the registry with secondary CBCLs were evaluated as well. These patients had either presented with both cutaneous and extracutaneous localizations (n = 35 patients) or had a history of systemic lymphoma prior to the development of skin lesions (n = 5 patients). Histologic classification (updated Kiel classification) had shown 3 centrocytic lymphomas, 5 centroblastic/centrocytic lymphomas, 20 centroblastic lymphomas, 2 immunoblastic lymphomas, 9 immunocytomas, and 1 plasmacytoma. In all patients, follow-up data were evaluated for CNS involvement. Wherever necessary, additional information was obtained from the referring clinician.

Results

Evaluation of follow-up data of 160 primary CBCLs revealed 4 patients who developed CNS involvement. This concerned 3 patients with PCFCCL and 1 patient with PCLBCL-leg. It is of interest to note that, in the group with PCFCCL, after a median survival of 49 months (range, 6-162 months), only 4 patients died of lymphoma and that 3 of these patients died of CNS involvement. In the group of 40 patients with secondary CBCLs, only 1 patient developed CNS involvement. Follow-up data and the relative frequency of CNS involvement for the different groups of CBCL are summarized in **Table 1**. The clinical details of the four primary CBCL patients who developed CNS involvement are summarized in **Table 2** and are discussed in more detail below.

Patient 1

A man age 65 years presented in 1990 with a solitary tumor with a greatest dimension of 4 cm on the left side of the chest. Histologic examination showed a diffuse proliferation of medium-sized to large centrocytes and centroblasts and was classified as a centroblastic/centrocytic lymphoma (updated Kiel classification). Staging procedures, including physical examination, complete blood cell counts, hepatic and renal function tests, chest radiography, abdominal CT, and bone marrow histology and cytology, did not show evidence of extracutaneous involvement. According to the EORTC classification, this patient was classified with a PCFCCL. Local electron beam radiotherapy (4 megaelectron volts [MeV]; cumulative dose,

40 grays [Gy] in 20 fractions) resulted in complete remission. The patient had two cutaneous recurrences on the forehead (after 40 months and 72 months) that were treated with local electron beam radiotherapy (4 MeV; cumulative dose, 20 Gy in 5 fractions), again resulting in a complete remission. In May 1997, 81 months after the initial diagnosis, the patient presented with severe headache, exophthalmus, and diplopia. A brain CT scan revealed an orbital mass on the right side spreading to the cavernous and sphenoid sinuses without evidence of

TABLE 1
Follow-Up Data on 168 Primary and 40 Secondary Cutaneous B-Cell Lymphomas Included in the Dutch Cutaneous Lymphoma Registry Between 1985 and 1998

	PCBCL (%)				
Characteristic	**PCFCCL**	**PCI**	**CLBCL-leg**	**Total**	**Secondary CBCL (%)**
No. of patients	122	16	22	160	40
Extracutaneous progression					
Total	7 of 122	1 of 16	12 of 22	20 of 160	Not relevant
CNS	3 of 122	0 of 16	1 of 22	4 of 160	1 of 40
Current status					
Alive	109 (90)	11 (69)	11 (50)	131 (82)	13 (32)
Died of unrelated cause	9 (7)	5 (31)	4 (18)	18 (11)	7 (18)
Died of lymphoma	4 (3)	0	7 (32)	11 (7)	20 (50)
Cause of death					
CNS involvement	3 of 4 (75)	0	1 of 7 (13)	4 of 11 (36)	1 of 20 (5)
Generalized disease	1 of 4 (25)	0	6 of 7 (87)	7 of 11 (64)	19 of 20 (95)

PCBCL: primary cutaneous B-cell lymphoma; PCFCCL: primary cutaneous follicle center cell lymphoma; CLBCL-leg: cutaneous large B-cell lymphoma presenting on the leg; CBCL: cutaneous B-cell lymphoma; CNS: central nervous system; PCI: Primary cutaneous immunocytoma.

TABLE 2
Clinical Data from Four Patients with Primary Cutaneous B-Cell Lymphoma Developing Central Nervous System Involvement

Characteristic	**Patient 1**	**Patient 2**	**Patient 3**	**Patient 4**
Gender/age (yrs)	M/65	M/68	F/66	F/71
Diagnosis	PCFCCL	PCFCCL	PCFCCL	PCLBCL-leg
Skin lesions at presentation	Tumor on the chest	Two tumors on the chest	Papules/nodules on left hip and buttock	Nodules and plaques on both lower legs
Therapy	RT	RT	None	COP
Result	CR	CR	CR	CR
Recurrence (months after diagnosis)	Skin (40) Skin (72) Orbita (81) CNS (93)	Bone (24) CNS (30)	CNS (6)	Skin (12) Skin (21) Skin (28) CNS (29)
Presenting neurologic symptoms	Gait instability	Lowered consciousness and left-sided facial paresis	Headache, disorientation, and left-sided homonymious hemianopia	Headache, paresis left arm, and right-sided ptosis
Therapy after CNS involvement	RT	Corticosteroids	Corticosteroids	Corticosteroids
Status (months of follow-up)	DOD (102)	DOD (31)	DOD (14)	DOD (34)
Survival after CNS involvement (months)	9	1	8	5
CT or MRI imaging	+	+	+	−
CSF examination	−	ND	+	+
Localization of CNS involvement	Parenchymatous	Parenchymatous	Leptomeningeal	Leptomeningeal

PCFCCL: primary cutaneous follicle center cell lymphoma; PCLBCL-leg: primary cutaneous large B-cell lymphoma of the leg; RT: radiotherapy; COP: cyclofosfamide, oncovin, and prednisone; corticosteroids: intravenous high dose corticosteroids; CR: complete remission; CNS: central nervous system; DOD: died of disease; CT: computerized tomography; MRI: magnetic resonance imaging; CSF: ceribrospinal fluid; ND: not done; +: evidence of lymphoma; −: no evidence of lymphoma.

bone destruction. Histologic examination showed a diffuse proliferation of centrocytes or centrocyte-like B-cells. Restaging did not reveal other lymphoma localizations. Cerebrospinal fluid examination (five samples) also was without abnormalities. Treatment with six cycles of multiagent chemotherapy (cyclophosphamide, doxorubicin, vincristine, and prednisone [CHOP]) combined with the intrathecal administration of methotrexate and prednisone again resulted in complete remission. However in, May 1998, the patient complained of gait instability. A CT scan showed an enhancing lesion in the right frontal region of the brain. Although there was no histologic confirmation of the lesion, a lymphoma localization was considered most likely because of the history of (recurrent) lymphoma, CNS signs, structural abnormalities on CT scan, and objective response to radiation treatment.[22] He was treated with hyperfractionated photon therapy (6 MeV; cumulative dose, 40 Gy), which resulted in partial remission. However, 9 months later, he was admitted again to the hospital because of lowered consciousness and diabetes insipidus due to a recurrence of the lesion. Apart from the CNS lesions, multiple lymphoma localizations were present in the cervical region. He died shortly after admission and had received treatment only with palliative measures. An autopsy was not performed.

Patient 2

In 1993, a man age 68 years presented with two slowly progressive tumors measuring 9 × 7 cm and 2 × 3 cm that were close to one another on the left side of the chest and had appeared 1 year earlier. Histologic examination showed a centroblastic-centrocytic lymphoma (updated Kiel classification). Staging procedures (see above) revealed no extracutaneous disease. According to the criteria of the EORTC classification, a diagnosis of PCFCCL was made. Treatment, consisting of surgical excision followed by electron beam radiotherapy (4 MeV; cumulative dose, 40 Gy in 20 fractions) of the affected skin area, resulted in complete remission. In September 1995, the patient complained about backache. An X-ray of the vertebral column showed osteolysis of the first lumbar vertebra. Histologic examination showed a B-cell lymphoma. Treatment with chlorambucil as monoagent chemotherapy resulted in a partial remission. In February 1996, 30 months after initial diagnosis, the patient was admitted to the hospital because of lowered consciousness with left-sided facial paresis. A CT scan of the brain revealed multiple cerebral lesions suggestive of lymphoma localizations. Examination of the cerebrospinal fluid was not performed. Despite treatment with high dose corticosteroids, his neurologic condition deteriorated, and he died 1 month later. Permission for an autopsy was not granted.

Patient 3

In 1996, a woman age 66 years presented with a 6-month history of progressive papules and nodules on both the left hip and the buttock. Histologic examination showed a diffuse

proliferation of centroblasts and admixed immunoblasts, which was classified as a centroblastic lymphoma, polymorphic subtype. There were no B symptoms. Her general medical history revealed urticaria, Morbus Sjögren, hypercholesterolemia, and cardiac arrhythmia. Extensive staging (see Patient 1) revealed no extracutaneous localizations. According to the EORTC classification, this patient was diagnosed with PCFCCL. Because all skin lesions had disappeared spontaneously after biopsy, no treatment was given. However, 6 months later, she was admitted to the hospital with headache, acute disorientation, and left-sided homonymous hemianopia. A CT scan of the brain showed a single lesion in the right parietooccipital area. Cytologic examination of the cerebrospinal fluid showed a population of CD20 positive, atypical B-cells. Treatment with high dose corticosteroids was initiated; however, gradually, her neurologic status worsened, and she died 8 months after CNS involvement was diagnosed. An autopsy was not performed.

Patient 4

A woman age 71 years presented in February 1994 with a 1-month-history of rapidly growing nodules and plaques on both lower legs. Histologic examination showed a diffuse large B-cell lymphoma with a mixed population of large centrocytes (large cleaved cells) and classical centroblasts. Staging did not show evidence of extracutaneous disease. There were no B symptoms. According to the EORTC classification, the diagnosis PCLBCL of the leg was made. Treatment with 8 cycles of multiagent chemotherapy (cyclophosphamide, vincristine, and prednisone), resulted in complete remission. Between February 1995 and September 1996, the patient had multiple skin recurrences that were treated subsequently with cyclofosfamide, mitoxantrone, oncovin, and prednisone; a combination of chlorambucil and prednisone with additional radiotherapy; and etopside. In October 1996, she was admitted to the hospital with headache, right-sided ptosis, and paresis of the left arm. A magnetic resonance image of the brain showed no abnormalities. However, examination of the cerebrospinal fluid revealed the presence of neoplastic CD20 positive B-cells. Treatment consisted of whole brain radiotherapy and high dose corticosteroids. Nevertheless, her neurologic status deteriorated, resulting in epileptic fits, followed by coma. She died in December 1996, 34 months after the initial diagnosis. An autopsy revealed only gliosis, probably due to the radiotherapy that was given shortly before death. The adrenal glands and a small part of the liver (near the gall bladder) were involved by lymphoma. No other lymphoma localizations were found.

Discussion

In the current report, we describe 4 patients with primary CBCL who developed CNS involvement. This group included 3 patients with PCFCCL and 1 patient with PCLBCL-leg. CNS involvement occurred after a median period of 30 months (range, 3-93 months) after the initial diagnosis and proved fatal after 1-9 months (median, 7 months). Presenting neurologic

complaints were headache, focal deficits, lowered consciousness, and disorientation.

Evaluation of follow-up data in the 122 patients with PCFCCL who were included in the Dutch registry revealed that only 7 patients had developed extracutaneous disease. In 3 of these 7 patients, dissemination to (peripheral) lymph nodes had occurred. Multiagent chemotherapy resulted in sustained complete remissions in all 3 patients. The other 4 patients died of lymphoma. It is noteworthy that 3 of these 4 patients died of CNS involvement. CNS involvement was the first manifestation of extracutaneous disease in 1 patient and was preceded by ocular or focal bone involvement in the other 2 patients. The fourth patient who died of disseminated PCFCCL also presented with neurologic symptoms (sensorimotor deficit and pain of the left leg) but was not considered to have CNS involvement. This patient had been in complete remission for more than 7 years after multiagent chemotherapy (six CHOP courses) because of a PCFCCL presenting on the back. In this patient, the neurologic symptoms were caused by a large abdominal mass invading the spinal column with spinal cord compression.

In the group of patients with PCLBCL-leg, which is known as a lymphoma with an intermediate prognosis, 7 of 22 patients (32%) died of lymphoma, but only 1 patient died with CNS involvement (Patient 4). In addition, of the 40 patients with secondary CBCL who had been included in the Dutch registry, 20 patients (50%) died of lymphoma, and involvement of the CNS had been observed in only 1 of them. This woman age 72 years had presented with slowly progressive plaques on the right lower leg that showed the histologic appearance of a B-immunoblastic lymphoma. However, because a bone marrow biopsy showed a population of small neoplastic B-cells, she was considered to have a secondary CBCL. The results of further staging procedures were completely negative. After several skin recurrences, but never evidence of extracutaneous disease (apart from the bone marrow mentioned above), she developed CNS involvement 41 months after diagnosis and died 1 month later. The initial treatment of patients who developed CNS involvement was not different (except for Patient 3) than in patients who showed no recurrences. Most patients received appropriate therapy for their lymphoma: radiotherapy for PCFCCL patients (Patients 1 and 2) and multiagent chemotherapy in multifocal PCLBCL-leg (Patient 4).[9] All patients reached a complete remission. Therefore, CNS involvement in this group of patients cannot be explained by differences in their treatment.

Data from literature suggest that the overall risk of secondary CNS involvement for patients with non-Hodgkin lymphoma is 6%.[23] Involvement of the eye, testis, peripheral blood, bone, bone marrow, or (para)-nasal sinuses by lymphoma has been reported to be a risk factor for dissemination to the CNS.[23] In another report, the involvement of two or more extralymph

node sites and elevated lactose dehydrogenase also were described as independent risk factors for CNS involvement.[24]

Reports on CNS involvement in patients with primary cutaneous lymphoma mainly concern cutaneous T-cell lymphoma, particularly in patients with advanced stages of mycosis fungoides.[13-18] In addition, in patients with intravascular large cell lymphoma, both the skin and the CNS are preferential sites of involvement.[19,20] However none of the four patients with a primary cutaneous intravascular large B-cell lymphoma who were included in the registry of the Dutch Cutaneous Lymphoma Group between 1985 and 1998 developed CNS involvement (data not shown). Reports on CNS involvement in patients with primary CBCL are extremely rare. Recently, a report on 4 patients with PCLBCL-leg mentioned briefly that, in 2 of these 4 patients, CNS involvement had occurred, but detailed information was not provided.[11] In addition, a patient with an extramedullary plasmacytoma presenting in the skin and disseminating to the CNS after a follow-up of 10 months has been reported.[25]

The prognosis of patients with non-Hodgkin lymphoma with secondary CNS involvement is poor. A median survival of only 2 months after CNS involvement has been reported,[26] even with intensive treatment. The patients in this study had a comparable median life expectancy of 7 months (range, 1-9 months) after CNS involvement was confirmed.

In conclusion, the results of the current study indicate that aproximately 2% of patients with primary CBCL may develop CNS involvement. However, major differences were found between patients with the different types of CBCL. In the group of patients with PCFCCL, in which extracutaneous dissemination and lymphoma-related mortality are rare, CNS involvement was noted in 3 of 7 patients (43%) who developed extracutaneous disease and accounted for 3 of 4 lymphoma-related deaths (75%). In contrast, in the group of patients with PCLBCL-leg and in the group of patients with secondary CBCL, mortality generally resulted from the presence of widespread disease and uncommonly was caused by CNS involvement. An explanation for the high frequency of CNS involvement in patients with PCFCCL developing extracutaneous disease is not readily available. It is of interest that dissemination in these lymphomas often involves extralymph node sites. For instance, in the 7 patients who showed extracutaneous spreading who were included in this study, dissemination to bone (4 patients), CNS (3 patients), kidney (1 patient), orbit (1 patient), and paranasal sinus (1 patient), was documented in addition to lymph nodes (4 patients). Involvement of two or more extralymph node sites is considered an independent risk factor.[24] Recent studies indicate that there is frequent CNS involvement in patients with primary mediastinal large B-cell lymphomas, which also showed a propensity to involve various extralymph node sites.[27] The molecular mechanisms underlying this peculiar dissemination pattern in the group of patients

with PCFCCL is unknown at present. In particular, adhesion molecules involved in CNS involvement by non-Hodgkin lymphomas have not been identified.

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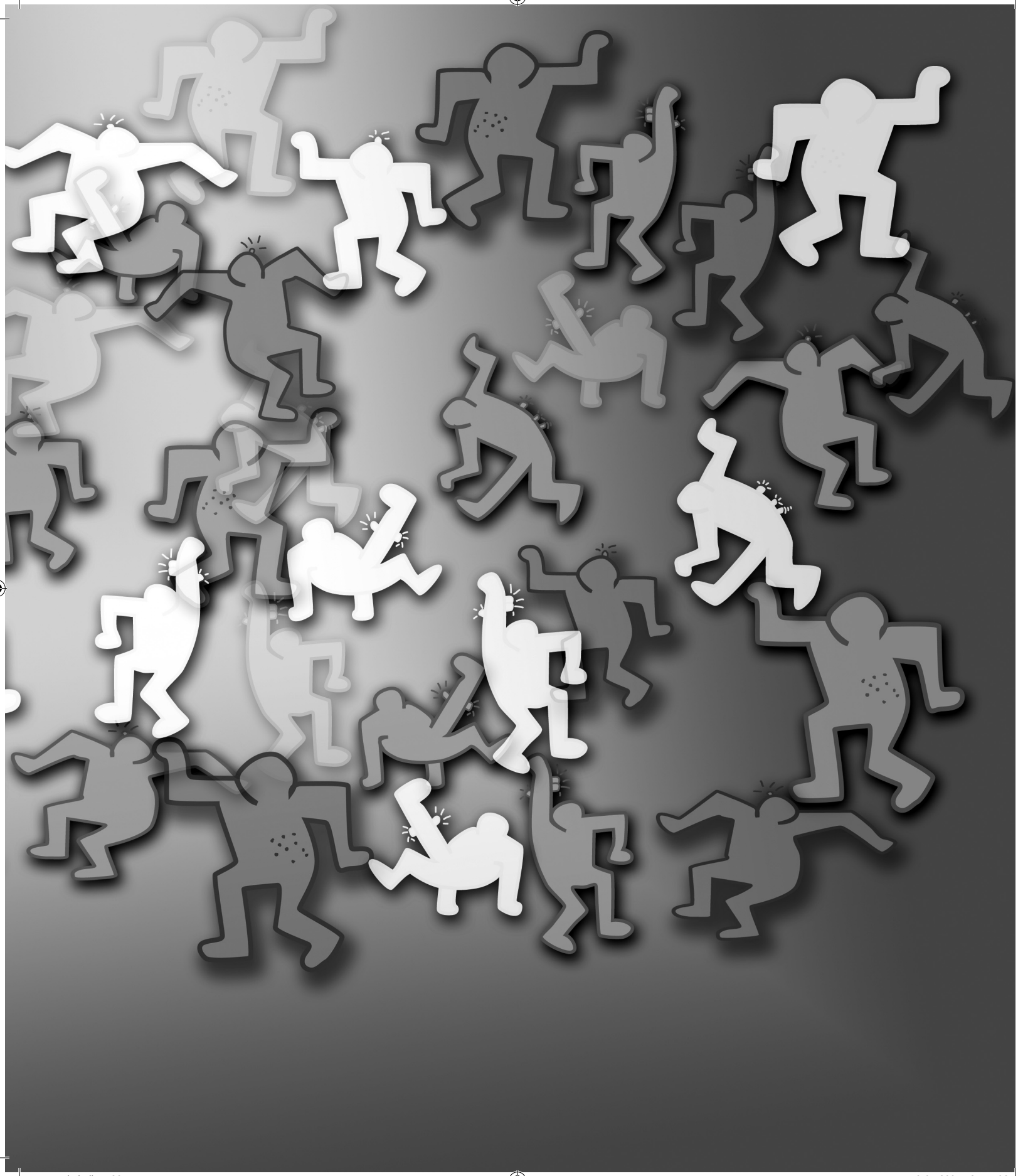

CHAPTER 9

General discussion

Nowadays cutaneous lymphomas can be classified by the EORTC or the WHO classification, but both systems have their shortcomings. The studies presented in this thesis have been focused particularly on those groups of cutaneous lymphomas that are classified differently in the EORTC and WHO classification. The initial goal of our studies was to formulate suggestions for an updated version of the EORTC classification. However, very recently discussions between representatives of the EORTC and the WHO group resulted in a new classification for cutaneous lymphomas. This new consensus classification is further referred to as the WHO-EORTC classification for cutaneous lymphomas.[1] In this chapter the results of our studies which made an important contribution to this new classification are discussed. In addition, guidelines for the treatment of different types of CTCL and CTCL are presented.

Classification of CTCL

Mycosis fungoides, variants of MF and Sézary's syndrome

Since there are no differences between the EORTC classification and the WHO classification regarding the terminology and classification of MF, MF variants and SS, these conditions will not further be discussed. In the WHO-EORTC classification the term MF-associated follicular mucinosis will be replaced by folliculotropic MF as a more appropriate term for this specific variant of MF. Moreover, the criteria for the diagnosis of SS have been modified and are now consistent with recent proposals of the International Society for Cutaneous Lymphomas.[2]

Primary cutaneous CD30-positive lymphoproliferative disorders

Both in the EORTC classification and in the WHO classification it is recognized that primary cutaneous CD30-positive lymphoproliferative disorders (CD30+ LPD) represent a spectrum of disease, which includes primary cutaneous CD30-positive (anaplastic) large T-cell lymphoma (LTCL), lymphomatoid papulosis (LyP), and borderline cases.[3,4] However, the different terms used for the primary cutaneous CD30-positive (anaplastic) LTCL in the EORTC and WHO classification has resulted in confusion, misclassification and inappropriate treatment.[5,6,7,8] Most cases of primary cutaneous CD30-positive LTCL have the morphology of large anaplastic cells, similar to those in systemic CD30-positive ALCL. However, in ca. 20% of cases they have a pleomorphic or immunoblastic (non-anaplastic) morphology.[9] Consistent with previous studies, our study presented in chapter 2 confirmed that there are no differences in clinical presentation and clinical behavior between anaplastic and non-anaplastic cases.[10] For that reason, in the EORTC classification the term primary cutaneous CD30-positive large T-cell lymphoma has always been preferred. This term emphasizes the importance of CD30 expression, c.q. differentiation from CD30-negative LTCL, and indicates that cytomorphology (anaplastic or non-anaplastic) is not important. In contrast, in the WHO classification the term cutaneous anaplastic large cell lymphoma (C-ALCL), as opposed to systemic ALC, is

Table 1. WHO-EORTC classification of cutaneous lymphomas

WHO-EORTC classification

Cutaneous T-cell lymphoma

Indolent clinical behaviour

Mycosis fungoides

MF variants

- Folliculotropic MF
- Pagetoid reticulosis
- Granulomatous slack skin

Primary cutaneous CD30+ lymphoproliferative disorders

- Primary cutaneous anaplastic large cell lymphoma
- Lymphomatoid papulosis

Subcutaneous panniculitis-like T-cell lymphoma

CTCL, small/medium-sized pleomorphic (CD4+) (provisional entity)

Aggressive clinical behaviour

Sézary syndrome

Adult T-cell leukemia/lymphoma

Extranodal NK/T-cell lymphoma, nasal-type

Primary cutaneous aggressive epidermotropic CD8+ cytotoxic T-cell lymphoma (provisional entity)

Cutaneous γ/δ-positive T-cell lymphoma (provisional entity)

Primary cutaneous peripheral T-cell lymphoma, unspecified

Precursor haematologic neoplasm

CD4+, CD56+ hematodermic neoplasm (blastic NK-cell lymphoma)

Cutaneous B-cell lymphoma

Indolent clinical behaviour

Primary cutaneous marginal zone B-cell lymphoma

Primary cutaneous follicle center lymphoma

Intermediate clinical behaviour

Primary cutaneous diffuse large B-cell lymphoma, leg-type

Primary cutaneous diffuse large B-cell lymphoma, other

Intravascular large B-cell lymphoma

used. This term has given the impression that cases with a non-anaplastic morphology do not belong to this group, but should be classified and thus treated as peripheral T-cell lymphoma, not otherwise specified (PTL, NOS).[5,7]

Nevertheless, consistent with the WHO terminology, in the WHO-EORTC classification the term C-ALCL will be used both for cases with an anaplastic and for cases with a non-anaplastic morphology. However, together with LyP these C-ALCL are part of a broad diagnostic category of primary cutaneous CD30+ LPD. Thus, consistent with the common practice within the Dutch Cutaneous Lymphoma group over the last ten years, differentiation is first made between primary cutaneous CD30+ LPD on the one hand, and systemic ALCL involving the skin secondarily and other types of CTCL expressing CD30 on the other. Based on the clinical behavior, ie the presence or absence of recurrent self-healing skin lesions distinction should then be made between LyP and C-ALCL Following this two step approach it becomes rather irrelevant whether the term primary cutaneous CD30-positive LTCL or C-ALCL is used, since cases have already been assigned to the group of primary cutaneous CD30+ LPD, which should guarantee appropriate (non-aggressive) treatment.

Classification of CTCL other than MF, SS and CD30+ LPD

The studies presented in chapters 3 and 4 were focused on the group of CTCL other than MF, SS and CD30+ LPD. The classification of this remaining group of CTCL is difficult and confusing, which is not surprising given the heterogeneity and rarity of these tumors. In the EORTC classification most of these lymphomas were grouped together in the group of primary cutaneous CD30-negative large T-cell lymphoma or in the provisional group of primary cutaneous small/medium-sized pleomorphic CTCL (**Table 2**). Distinction between the two categories, which was based on the presence of more or less than 30% large neoplastic T-cells, was considered useful because several studies demonstrated a significant difference in survival between these two groups.[3,11,12,13] However, our studies presented in chapter 3 suggest that this more favorable prognosis is restricted to small/medium-sized pleomorphic CTCL with a CD4+ T-cell phenotype, in particular when presenting with localized disease, but does not hold true for cases with a CD8+ T-cell phenotype.[14] In CD8+ CTCL (non-MF) no difference in clinical behaviour and outcome was seen between cases with a small cell or large cell morphology.[14] Moreover, the EORTC category of CD30-negative large cell CTCL has become quite heterogeneous by the recognition of new diagnostic categories, such as different types of subcutaneous panniculitis-like T-cell lymphoma (SPTL), extranodal NK/T-cell lymphoma, nasal-type, CD4+, CD56+ hematodermic neoplasm (formerly also designated as blastic NK-cell lymphoma), primary cutaneous aggressive epidermotropic CD8-positive cytotoxic T-cell lymphoma and cutaneous gamma/delta positive T-cell lymphoma.[15] In the WHO classification SPTL, nasal-type NK/T-cell lymphoma and blastic NK-cell lymphoma were included as separate

entities, whereas the other entities are included in the broad category of PTL, NOS (see **Table 2**).

In the WHO-EORTC classification extranodal NK/T-cell lymphoma, nasal-type and CD4+, CD56+ hematodermic neoplasm (blastic NK-cell lymphoma in the WHO classification) are also included as separate entities. In chapter 4 a large group of CD56+ cutaneous NK/T-cell lymphoma, nasal-type and CD4+, CD56+ hematodermic neoplasms (blastic NK-cell lymphomas) was evaluated.[16] In the group of extranodal NK/T-cell lymphoma, nasal-type the skin is the second most common site of involvement after the nasal cavity/ nasopharynx. Skin lesions are generally a secondary manifestation of the disease, but rare primary cutaneous cases have been reported as well. The most important factor predicting poor outcome was the presence of extracutaneous involvement at presentation. In patients presenting with only skin lesions a median survival of 27 months was found, compared to 5 months for patients presenting with cutaneous and extracutaneous disease. However, all patients with nasal-type NK/T-cell lymphoma presenting in the skin should be considered to have aggressive disease, which is commonly resistant to conventional chemotherapy.

CD4+, CD56+ hematodermic neoplasms (blastic NK-cell lymphomas) frequently present in the skin with or without extracutaneous disease. However, in patients presenting with only skin lesions rapid involvement of bone marrow, peripheral blood, lymph nodes and extranodal sites is the rule. In our study presented in chapter 4 patients presenting with only skin lesions had a slightly better prognosis than patients presenting with both cutaneous and extracutaneous disease (median survival 21 versus 12 months, respectively).

Comparison between CD4+, CD56+ hematodermic neoplasms and CD56+ myelomonocytic leukemias presenting in the skin showed striking similarities in histology, immunophenotype and clinical presentation, including the percentage of bone marrow involvement at presentation and prognosis. Consistently, recent studies suggested that these CD4+, CD56+ hematodermic neoplasms are conceptually similar to so-called "aleukemic leukemia cutis".[15]
The overlapping clinical, histological and immunophenotypical features between CD4+, CD56+ hematodermic neoplasms and CD56+ myeloid leukemias presenting in the skin suggest that both conditions are closely related and also provide a rationale to treat these patients with more aggressive regimens used in myeloid leukemias rather than with conventional CHOP(-like) regimens.

With respect to the group of SPTL recent studies showed both clinical, histological and immunophenotypical differences between cases with an α/β T-cell phenotype and cases with a γ/δ T-cell phenotype, suggesting that these may represent different entities. Whereas SPTL

with an α/β T-cell phenotype represent a homogeneous group with in many patients a rather indolent clinical behaviour, SPTL with a γ/δ T-cell phenotype overlap with other types of γ/δ –positive T-cell lymphoma and invariably run a very aggressive clinical course.[15,17-20] In the WHO-EORTC the term SPTL is restricted for SPTL with an α/β T-cell phenotype.[15]

With respect to the original group of PTL, NOS in the WHO classification, there was consensus that primary cutaneous small-medium CD4+ T-cell lymphoma, primary cutaneous aggressive epidermotropic CD8+ cytotoxic T-cell lymphoma and cutaneous gamma-delta positive T-cell lymphoma can be separated out as provisional disease entities. This latter group also includes SPTL with a gamma/delta phenotype. In the WHO-EORTC classification the term *PTL, unspecified* is maintained for cases not belonging to either of these entities. This group includes cases classified as primary cutaneous CD30-negative large T-cell lymphomas in the EORTC classification and a small group of unclassifiable CTCL.

Classification of CBCL

Primary cutaneous marginal zone B-cell lymphoma

As already indicated in chapter 1, the term primary cutaneous marginal zone B-cell lymphoma (PCMZL) is nowadays preferred for post-germinal center B-cell neoplasms composed of variable numbers of marginal zone cells, lymphoplasmacytoid cells and plasma cells. Also in the WHO-EORTC classification the term PCMZL is used. Moreover, exceptional cases of primary cutaneous plasmacytoma, (extramedullary plasmacytoma of the skin), included as a provisional entity in the EORTC classification, show considerable overlap with PCMZL, and is therefore included in the spectrum of PCMZL.

Primary cutaneous follicle center cell lymphoma and primary cutaneous large B-cell lymphoma of the leg

In the EORTC classification primary cutaneous follicle center cell lymphomas (PCFCCL) and primary cutaneous large B-cell lymphoma of the leg (PCLBCL-leg) are recognized as distinct entities. PCFCCL are characterized by a proliferation of small and more often large centrocytes with a follicular and more a commonly a diffuse growth pattern, and clinically by the presence of localized skin lesions mostly on the head or trunk and an excellent prognosis. PCLBCL-leg is characterized by a diffuse proliferation of centroblasts and immunoblasts, and skin tumors on the (lower) legs in particular in elderly females and an intermediate prognosis. In contrast to PCFCCL, these PCLBCL-leg almost consistently show strong expression of bcl-2 and Mum-1/IRF4.[21,22]

The WHO did not adopt these entities. In this classification PCFCCL with a (partly) follicular growth pattern are classified as cutaneous follicle center lymphoma, whereas PCFCCL with a diffuse proliferation of large centrocytes are classified as diffuse large B-cell lymphoma.

PCLBCL-leg cases are also classified as diffuse large B-cell lymphoma. The distinction between two types of PCLBCL primarily on the basis of site has been much disputed,[8,22] and was the main reason to perform a European multicenter study on a large group of PCLBCL. The results of this study described in chapter 6, confirmed that PCLBCL-leg and PCFCCL with a diffuse large cell histology are distinct entities.[23] In addition, a predominance of tumor cells with round nuclei (centroblasts and immunoblasts) was found to be an adverse prognostic factor in both groups, whereas the presence of multiple skin lesions was associated with a poor prognosis only in patients with a PCLBCL-leg, but not in patients with a PCFCCL.
In the WHO-EORTC classification it is recognized that PCFCCL as defined in the EORTC classification indeed form a spectrum of disease which includes cases with a follicular, a follicular and diffuse and a diffuse growth pattern. This group will further be referred to as *primary cutaneous follicle center lymphoma*. However, in contrast to the EORTC classification tumors showing a diffuse proliferation of centroblasts and immunoblasts not arising on the leg are no longer classified as PCFCL, but as PCLBCL, which is in line with the results of our study described in chapter 6. Thus it is acknowledged that, while most cases showing a diffuse proliferation of centroblasts and immunoblasts and strong expression of bcl-2 and Mum-1/IRF4 are localized on the leg, cases with a similar morphology and immunophenotype may sometimes arise at sites other than the leg.[23] In the WHO-EORTC classification the term *PCLBCL, leg type* is proposed for both lesions on the legs and similar lesions at other skin sites. In addition, the term *PCLBCL, other* is introduced for rare cases of PCLBCL not belonging to the group of PCLBCL, leg type or PCFCL with a diffuse growth pattern. This group includes rare morphologic variants of PCLBCL, such as anaplastic and plasmablastic variants and T-cell/histiocytes-rich large B-cell lymphoma and rare cases of primary cutaneous intravascular large B-cell lymphoma (see **Table 1**).

Guidelines for the treatment of cutaneous lymphomas

One of the goals of the studies presented in this thesis was to define therapeutic guidelines for the different types of primary cutaneous lymphoma. Specific questions concerned the treatment of a) primary cutaneous CD30-positive LTCL presenting with multifocal skin lesions (chapter 2), b) CTCL other than MF, SS and CD30+ LPD, and c) CBCL presenting with multifocal skin lesions. The main results and conclusions of these studies are briefly discussed below. Based on the results of these studies, the therapeutic guidelines of the Dutch Cutaneous Lymphoma Group and other national guidelines published recently,[24,25] the first choice of treatment and alternative therapies for the different types of cutaneous lymphoma included in the WHO-EORTC classification are summarized in **Tables 2** and **3**.

Primary cutaneous CD30-positive LTCL presenting with multifocal skin lesions

There is almost general agreement that patients with a primary cutaneous CD30+ LTCL

Table 2. Therapeutic guidelines for most common types of cutaneous lymphoma according to the WHO-EORTC classification

WHO-EORTC Classification		First line	Second line	Experimental
Cutaneous T-cell lymphoma				
Mycosis fungoides	Limited patches and plaques (<10% skin surface)	PUVA; topical steroids	UV-B/UV-B narrow band Topical chemotherapy (1)	Bexarotene gel (2)
	Generalized patches/plaques (>10% skin surface)	PUVA	Topical chemotherapy; TSEB; PUVA + IFNα or retinoids	Denileukin diftitox (Ontak) (2) Bexarotene
	Tumor stage	PUVA + RT; TSEB	PUVA + IFNα or retinoids Systemic chemotherapy	Denileukin diftitox (Ontak) (2) PBSCT
	Lymph node involvement	TSEB/RT Systemic chemotherapy	Systemic chemotherapy	Denileukin diftitox (2) Alemtuzumab; PBSCT
	Visceral involvement	Systemic chemotherapy	Systemic chemotherapy	Denileukin diftitox (Ontak) (2) Alemtuzumab (Campath-1H); PBSCT
Folliculotropic MF		See tumor stage MF		
Pagetoid reticulosis		Radiotherapy	PUVA	
Granulomatous slack skin		Radiotherapy; Excision		
Sézary syndrome-		Photopheresis (3) +/- IFNα Chlorambucil/prednisone	Methotrexate; bexarotene; Systemic chemotherapy	Denileukin diftitox (Ontak) (2) PBSCT; Alemtuzumab (anti-CD52)
Primary cutaneous anaplastic large cell lymphoma		Radiotherapy; excision; methotrexate (multifocal)	Systemic chemotherapy	Anti-CD30 moab
Lymphomatoid papulosis		Wait & see	Methotrexate; PUVA; topical chemotherpy	
Subcutaneous panniculitis-like TCL (α/β T-cell)		Oral steroids	Systemic chemotherapy; RT	
CTCL, small/medium-sized pleomorphic (CD4+)		Radiotherapy; excision, Systemic chemotherapy	IFNα; cyclophophamide (multifocal)	
extranodal NK/T-cell lymphoma, nasal type				
aggressive CD8+ CTCL				PBSCT
Cutaneous γ/δ-positive T-cell lymphoma				
Primary cutaneous PTL, unspecified				
CD4+, CD56+ hematodermic neoplasm		Treat as acute leukemia		
Cutaneous B-cell lymphoma				
Primary cutaneous marginal zone B-cell lymphoma		RT; excision (solitary) Chlorambucil (multifocal)	intralesional/ systemic IFNα; prednisone; systemic chemotherapy	Antibiotics; Intralesional rituximab Radiotherapy (2x2 Gy)
Primary cutaneous follicle center lymphoma		RT	ntralesional IFNα; systemic chemotherapy	Intralesional/ systemic rituximab
Primary cutaneous diffuse large B-cell lymphoma, leg type and other (incl. primary cutaneous intravascular B-cell lymphoma		Systemic chemotherapy	CHOP + rituximab RT (small, solitary lesion)	

Legend:
(1): topical nitrogen mustard or carmustine (BCNU)
(2): not registered in the Netherlands;
(3): not available in the Netherlands;
TSEB: total skin electron beam radiotherapy;
RT: radiotherapy;
IFNα: interferon alpha;
PBSCT: peripheral blood stem cell transplantation;
moab: monoclonal antibody;
CHOP: cyclophosphamide, doxorubicin, vincristine, prednisone.

presenting with localized skin lesions can best be treated with radiotherapy or, in case of a solitary tumor, even with simple excision. However, the treatment of patients presenting with multifocal skin lesions was more controversial. According to the 1991 guidelines of the Dutch Cutaneous Lymphoma Group such patients should be treated with doxorubicin-based multi-agent chemotherapy. However, the results of our studies presented in chapter 2 demonstrated that all patients who were treated with CHOP courses because of multifocal skin lesions had one or several skin relapses afterwards.[26] These results indicate that skin-limited CD30+ LTCL with multifocal skin lesions should not be treated routinely with systemic chemotherapy, but can better be treated with radiotherapy in case of only few skin lesions or low-dose methotrexate as in LyP.[27,28] Multiagent chemotherapy is only indicated in patients with or developing extracutaneous disease, or rare cases with progressive skin lesions that can not be controlled in other ways.

CTCL other than MF, SS and CD30+ LPD

With the exception of the group of SPTL (with an α/β T-cell phenotype) and the group of primary cutaneous small-medium CD4+ T-cell lymphoma, all entities within this category have a very poor prognosis, also in cases presenting with only skin lesions. Therefore, distinction between "primary" and "secondary" cutaneous involvement seems less important than for other types of malignant lymphoma involving the skin.

Patients with a SPTL are generally treated with chemotherapy and radiotherapy. However, recent studies suggest that many patients can be controlled for long periods of time with systemic corticosteroids.[15,19] Patients presenting with a solitary tumor can be treated with radiotherapy.

In patients with a CD4+ small/medium pleomorphic CTCL presenting with solitary localized skin lesions surgical excision or radiotherapy is the preferred mode of treatment. Cyclophosphamide as single-agent therapy and interferon alpha have been reported effective in patients with more generalized skin disease.[29] However, the optimal treatment for this group has still to be defined.

Other types of cutaneous T- and NK-cell lymphomas in this category are generally treated with doxorubicin-based multi-agent chemotherapy, but the results are often disappointing.

In patients with a CD4+, CD56+ hematodermic neoplasm systemic chemotherapy usually results in a complete remission, but quick relapses unresponsive to further chemotherapy are the rule. Recent studies suggest that patients can best be treated with regimens used in acute leukemias. Both in our study[30] as in recent studies by other authors[31,32] the best results were seen in patients treated with allogeneic bone marrow transplantation.

CBCL presenting with multifocal skin lesions

In patients with a PCFCL or PCMZL presenting with localized skin lesions radiotherapy is the preferred mode of treatment.[26,33] The results of our studies presented in chapter 7 suggest

that patients with a PCFCL or PCMZL presenting with multifocal skin lesions have the same excellent prognosis as patients presenting with localized disease, and that radiotherapy directed towards all skin lesions is as effective as multi-agent chemotherapy. Only in patients with very extensive cutaneous disease, patients with extremely thick skin tumors and patients developing extracutaneous disease systemic chemotherapy is required.[23,26] Patients with PCLBCL, leg type which are in many ways similar to other systemic diffuse large B-cell lymphomas, should always be treated with doxorubicin-based multi-agent chemotherapy. By exception patients presenting with a small solitary tumor can be treated with radiotherapy. Recent studies report beneficial effects of systemic of intralesional administration of anti-CD20 antibody (Rituximab) therapy in small series of PCFCL and PCLBCL, leg type, but long-term follow-up data are not available and the place of rituximab in the treatment of PCLBCL, either as single agent therapy or in combination with systemic chemotherapy remains to be established.[34,35]

Conclusion and future directions

The studies presented in this thesis, aimed at improved guidelines for the classification and treatment of cutaneous lymphomas, have contributed to a new classification for cutaneous lymphomas. This WHO-EORTC classification is expected to contribute to a more uniform diagnosis and hence a more uniform treatment of patients with a cutaneous lymphoma.

The new definitions of the group of PCFCL, PCLBCL leg-type and PCLBCL, other will allow a more reliable distinction between indolent and more aggressive types of CBCL, and facilitate the decision whether radiotherapy or systemic chemotherapy should be selected as first choice of treatment. Large multicenter studies are now required to validate the current proposals, and in particular to investigate the diagnostic and prognostic value of bcl-2 and Mum-1/IRF4 protein expression.[22,36]

The classification of CTCL other than MF, SS and the group of primary cutaneous CD30-positive LPD is still difficult, as it requires accurate clinicopathologic correlation and a number of complementary techniques to arrive at a definite diagnosis. Apart from the group of SPTL and the group of CD4+ small/medium-sized pleomorphic CTCL these rare types of CTCL have a very poor prognosis and are generally resistant to conventional chemotherapy. More aggressive regimens, including allogeneic bone marrow transplantation, are currently under investigation. Recently, studies have started to investigate gene and protein expression profiles in different types of (cutaneous) lymphoma.[37] It is expected that these studies will not only contribute to a better understanding of the molecular pathways involved in the development and progression of these lymphomas, but will also provide new molecular targets for diagnosis and therapeutic intervention as well as more refined classification schemes.

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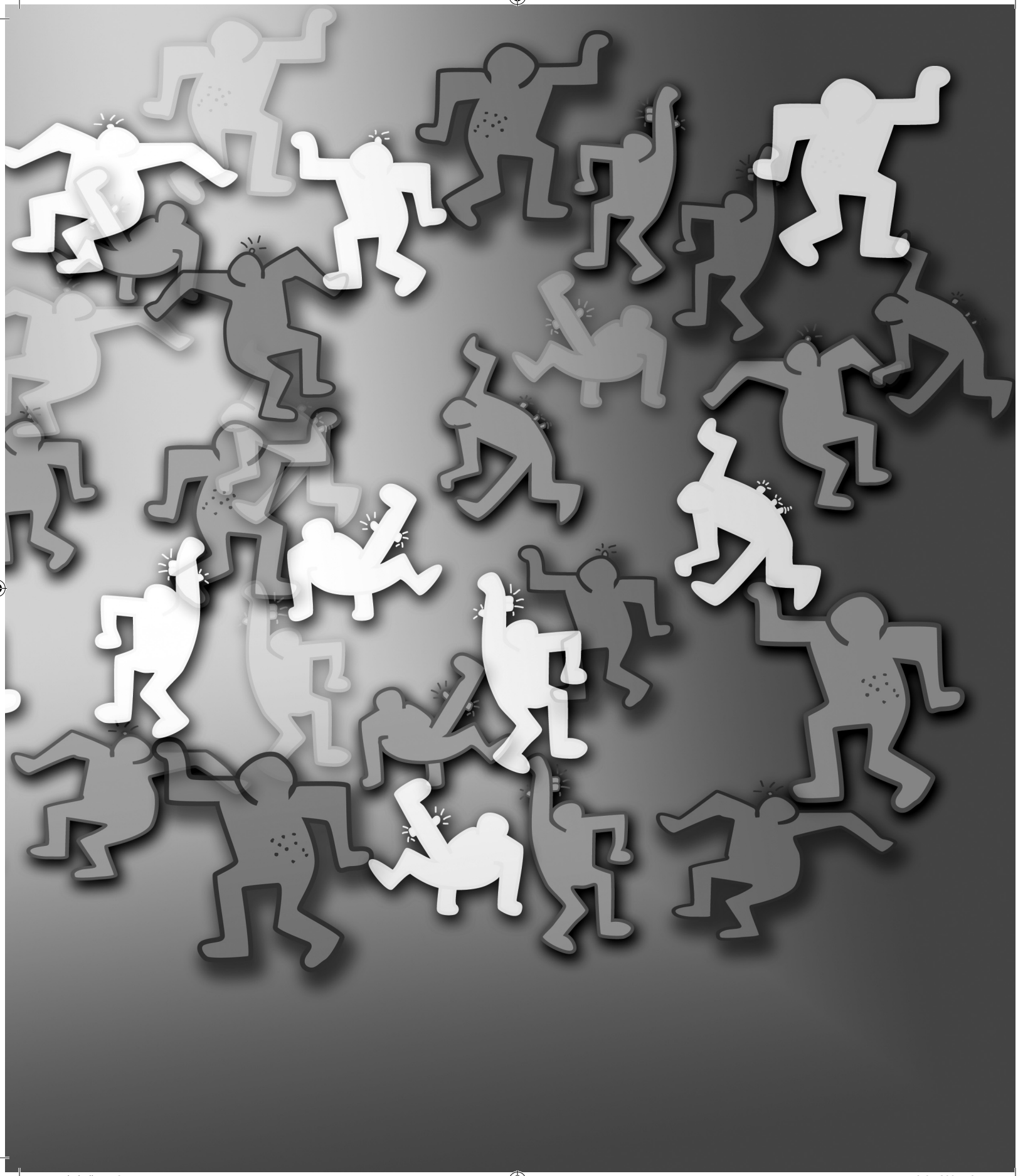

CHAPTER 10

Summary

Primary cutaneous lymphoma form a seperate group of non-Hodgkin lymphoma. Apart from the usual nodal presentation of a lymphoma, less frequently a lymphoma develops in an extranodal site. The skin is, after the gastrointestinal tract, the most frequent site of extranodal lymphoma. If the skin is the primary site of involvement, i.e. no extracutaneous sites are involved at diagnosis, these lymphomas are called primary cutaneous lymphoma. In this thesis different types of primary cutaneous lymphoma are evaluated and discussed. In chapter 2 a large group of primary cutaneous CD30+ lympoproliferations is described and compared with a group of systemic CD30+ ALCL with skin localisations. Lymphomatoid papulosis and primary cutaneous CD30+ CTCL are closely related conditions and should be considered as a spectrum, with a comparable, excellent, prognosis. Multiagent chemotherapy (MAC) could not induce long lasting remissions, in fact all patients treated with MAC developed one or more (cutaneous) relapses. Therefor MAC is only indicated in case of extracuteneous localisations. In chapter 3 a group of CD30-negative T-cell lymphomas presenting in the skin that could not be diagnosed as MF, SS or SPTL are evaluated. In this group there were few survivors, apart from a rare group of patients with primary cutaneous lymphoma with small-medium sized CD4+/CD8-neoplastic T-cells (less than 30% large cells). In particular, patients with localized disease had an excellent prognosis. In chapter 4 haematological malignancies presenting in the skin and expressing CD56 were collected, both from the Dutch cutaneous lymphoma group and literature. In general these types of malignancies had a poor prognosis, except for patients with primary cutaneous CD30+ LPD, that showed a similar good prognosis as CD56-negative cases. Most cases belonged to the group of nasal-type NK/T-cell lymphoma and the group of CD4+, CD56+ hematodermic neoplasm (formerly also designated as blastic NK-cell lymphoma. In addition, CD56 was expressed in some SPTL, rare primary cutaneous CD30-negative large T-cell lymphomas, skin localisations of acute myeloid leukemia and CD30+ CTCL. In most of these groups CD56 expression did not affect prognosis. However, in SPTL CD56 expression proved a marker for gamma/delta T-cell origin and these cases showed a poorer prognosis as compared to SPTL with an alpha/beta phenotype (that were usually CD56-negative). In the new WHO-EORTC classification the category of SPTL only includes cases with an alpha/beta-positive phenotype, whereas cases with a gamma/delta positive phenotype are included in the provisional category of cutaneous gamma/delta-positive T-cell lymphoma. In chapter 5 a rare case of lymphomatoid papulosis with CD56-expression was presented and the frequency of co-expression of CD56 in primary

cutaneous CD30+ LPD was analyzed. CD56 expression was found in approximately 10% of CD30+ LPD (both LyP and primary CD30+ CTCL). However, these CD56+ cases were not found to have a different prognosis from CD56 negative cases.

In chapter 6 a European multicenter study on primary cutaneous large B-cell lymphomas is presented. Patients with primary cutaneous large B-cell lymphoma of the leg showed a poorer prognosis as patients with primary cutaneous follicle center cell lymphoma (PCFCCL). Moreover, round cell morphology was identified as a poor prognostic parameter. Although this was closely related to presentation on the leg(s), also in the group of PCFCCL the presence of a predominance of cells with round nuclei (centroblasts and immunoblasts) was associated with a poorer prognosis. The results of this study contributed to a new category in the WHO-EORTC classification, designated primary cutaneous large B-cell lymphoma (PCLBCL), leg-type, indicating that both patients with the classical presentation on the leg(s) as patients showing the same morphology and immunophenotype (bcl-2+, Mum-1/IRF4+) on other sites are included in this group. Presentation with multifocal lesions proved to be a poor prognostic parameter for PCLBCL-leg-type, but not for PCFCCL. In chapter 7 treatment results in multifocal primary CBCL were analyzed. The main question in this study was if PCFCCL presenting with multifocal skin lesions should be treated with MAC. The study showed that MAC is only indicated in PCLBCL, leg-type and not in (multifocal) PCFCCL. Radiotherapy on multiple sites appeared equally effective as MAC in these patients. In chapter 8 the frequency of CNS-involvement in CBCL patients of the Dutch cutaneous lymphoma group. was evaluated. The frequency was low. Only 4/140 patients with a primary CBCL developed CNS involvement in the course of their disease. Interestingly 3 of these 4 patients were PCFCCL, a lymphoma usually with an excellent prognosis. Only 4 disease related deaths were reported in this group of which 3 with CNS involvement. The reason for this relatively high prevalence of CNS involvement in PCFCCL is unclear.

The studies presented in this thesis have provided important information, which has contributed to the recent development of the WHO-EORTC classification. Moreover, they have contributed to updated guidelines for the treatment of the different types of primary cutaneous lymphomas, as presented in **TABLE 2** in chapter 9.

Samenvatting voor de leek

Maligne lymfomen zijn kwaadaardige woekeringen van verschillende typen witte bloedcellen. Deze aandoeningen ontstaan meestal in lymfklieren (lymfklierkanker), maar in ca. 40% van de patiënten komen deze voor het eerst tot uiting in zogenaamde extranodale organen, zoals het maagdarmstelsel of de huid. Het in dit proefschrift beschreven onderzoek is met name gericht op zogenaamde primair cutane lymfomen, dat wil zeggen maligne lymfomen die zich in de huid presenteren en waarbij bij nader onderzoek (stagering) geen andere localisaties gevonden worden. Deze groep is erg heterogeen en bestaat uit entiteiten afkomstig van verschillende types witte bloedcellen. Het grootst is de groep van cutane T-cel lymfomen (ca. 75%), daarna de groep van cutane B-cel lymfomen (ca. 20%) en slechts incidenteel wordt een NK-cel origine of overige/onbekende vroege voorlopercel origine gevonden. Een groot aantal van deze primair cutane lymfomen waren goed gekarakteriseerd in de EORTC classificatie. Een groot deel van, vooral Amerikaanse, artsen gebruikte voor primaire cutane lymfomen echter de REAL classificatie, die nauwelijks oog had voor de specifieke diagnostiek en behandeling van deze lymfomen. Haar opvolger de WHO classificatie had duidelijk meer aandacht voor primaire cutane lymfomen en een groot gedeelte van de EORTC classificatie werd overgenomen in deze classificatie. Ondanks de sterk verbeterde aandacht voor primair cutane lymfomen bleef er discrepantie en discussie over diagnostiek en behandeling van een aantal primair cutane lymfomen. Aangezien de benaming van lymfomen veelal direct resulteert in een specifieke behandeling, is classificatie meer dan een academische discussie. In dit proefschrift worden de voor- en nadelen van de EORTC en de WHO schema's bij de classificatie van de verschillende typen primair cutane lymfomen onderzocht. Tevens werden de bestaande behandelingsprotocollen van een aantal groepen kritisch geëvalueerd.

In hoofdstuk 2 wordt het spectrum van primair cutane CD30-positieve cutane lymfomen besproken. Deze groep blijkt een uitstekende prognose te hebben, onafhankelijk van verschillende klinische en histologische parameters. Chemotherapie heeft nagenoeg geen plaats binnen deze groep wanneer er enkel huidafwijkingen zijn. In tegenstelling tot deze groep met gunstige prognose bestaat er een groep van CD30-negatieve T-cel lymfomen (hoofdstuk 3), die niet als mycosis fungoïdes of Sézary syndroom kunnen worden geclassificeerd. Deze heterogene groep blijkt een slechte prognose te hebben met uitzondering van, vooral op een beperkt gebied van de huid gelokaliseerde, CD4+/CD8- klein tot middelgrootcellige primair cutane T-cel lymfomen. De prognose voor de overige patiënten met een dergelijk CD30-negatief T-cel lymfoom is slecht, ook wanneer intensieve chemotherapie wordt gegeven. Nieuwe therapieën moeten dan ook worden gezocht. In hoofdstuk 4 wordt een relatief nieuwe groep cutane lymfomen beschreven, die nog niet apart vermeld werd in de EORTC classificatie. Binnen deze CD56+ cutane lymfomen blijken klinisch en histologisch goed afgrensbare groepen te bestaan. De belangrijkste zijn het NK/T-cel lymfoom en het blastair

NK-cel lymfoom (tegenwoordig meestal CD4+CD56+ haematodermic neoplasm genoemd). Daarnaast kan CD56 tot expressie komen bij bekende typen cutane T-cel lymfomen en huidlokalisaties van een myeloide leukemie. Alle genoemde groepen hebben over het algemeen een zeer slechte prognose. Uitzondering hierop zijn primair cutaan CD30+ lymfomen en lymfomatoide papulose die ook met co-expressie van CD56 hun uitstekende prognose blijven behouden (hoofdstuk 5).

Binnen de groep primair cutane B-cel lymfomen was vooral de subclassificatie van het grootcellig B-cel lymfoom van het been in de EORTC classificatie reden tot veel ophef. Een studie in samenwerking met een aantal Europese instituten (hoofdstuk 6), beschrijft de verschillende risicofactoren waarbij het grootcellig B-cel lymfoom van het been inderdaad een slechtere prognose te hebben. Naast de lokalisatie op het been blijkt de morfologie van de tumorcellen sterk gecorreleerd met de lokalisatie en dus ook prognose. In hoofdstuk 7 wordt de behandeling van multifocale B-cel lymfomen besproken. In tegenstelling tot de oude consensus van de Nederlandse Werkgroep Cutane Lymfomen blijkt bij alle B-cel lymfomen, behalve het grootcellig B-cel lymfoom op het been, lokaal radiotherapie afdoende te zijn. Bij het grootcellig B-cel lymfoom van het been is alleen bij een kleine solitaire tumor radiotherapie te overwegen, maar bij meerdere laesies is chemotherapie geïndiceerd. De prognose blijkt dan ook slechter bij multipele laesies bij een grootcellig B-cel lymfoom op het been, terwijl bij de andere types de prognose even goed blijft. Tijdens het verzamelen van de follow-up gegevens voor hoofdstuk 6 en 7 werd bij een aantal patiënten uitzaaiing naar het centraal zenuwstelsel (CZS) gemeld. Lokalisaties in het CZS werden nooit eerder in de literatuur gemeld en zijn nu beschreven in hoofdstuk 8. Recidieven buiten de huid van het primair cutane B-cel lymfoom zijn zeldzaam en opvallend vaak bleek dan juist het CZS aangedaan, vooral bij het primair cutaan follikel centrum cel lymfoom. Een verklaring hiervoor is nog niet gevonden.

De artikelen beschreven in dit proefschrift hebben een belangrijke rol gespeeld bij consensus bijeenkomsten, waarbij door vertegenwoordigers van de EORTC en van de WHO classificatie een nieuwe classificatie is opgesteld: de WHO-EORTC classificatie. Tevens hebben de resultaten van de in dit proefschrift beschreven studies geleid tot nieuwe richtlijnen voor behandeling van verschillende typen van primair cutane lymfomen.

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Curriculum vitae

De schrijver van dit proefschrift werd op 2 maart 1970 te Schoonhoven geboren. In 1989 behaalde hij het einddiploma VWO aan het Stedelijk Gymnasium te 's Hertogenbosch. In hetzelfde jaar begon hij met de studie Geneeskunde aan de Vrije Universiteit te Amsterdam. Tijdens de laatste drie jaren voor zijn co-schappen werd onderzoek naar geneesmiddelresistentie bij kinderleukemie gedaan op de afdeling kindergeneeskunde en oncologie in het Academisch Ziekenhuis der Vrije Universitei te Amsterdam onder leiding van Rob Pieters, Gerrit Jansen en Frits Peters. In 1995 werd dit onderzoek deels op de Dipartimento di Farmacologia preclinica e clinica, Universita degli studi di Firenze (Florence), onder leiding van van Prof. dr. Enrico Mini verricht. Na het afstuderen in 1998 werkte hij kortdurend als arts-assistent Interne Geneeskunde in het Ziekenhuis Hilversum te Hilversum en hierna als arts-assistent Dermatologie in het Academisch Ziekenhuis der Vrije Universitei te Amsterdam (hoofd: Prof. dr. Th. M. Starink).
In 2000 begon hij als arts-assistent in het Leids Universitair Medisch Centrum (hoofd: Prof. dr. R. Willemze), waar op 1 februari 2001 werd begonnen met de opleiding tot huidarts. Dit proefschrift beschrijft werk dat in Amsterdam is gestart en is voortgezet in Leiden onder supervisie van Prof. dr. R. Willemze en Prof. dr. C. J. L. M. Meijer. Vanaf april 2005 zal hij gaan werken als dermatoloog in het Reinier de Graaf Gasthuis in Delft.

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