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Title: Cutaneous CD30-positive lymphoproliferations: clinical and molecular aspects and differential diagnosis  
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General introduction
PRIMARY CUTANEOUS T-CELL LYMPHOMAS

Primary cutaneous lymphomas represent a heterogeneous group of malignant non-Hodgkin lymphomas that clinically originate in the skin with no evidence of extracutaneous disease at the time of diagnosis. The incidence is being estimated on 1:100,000 individuals per year. Primary cutaneous lymphomas often differ in clinical behavior, prognosis and biological features from their histologically similar nodal counterparts with or without secondary skin involvement, indicating a different pathogenesis and requiring a different treatment. For these reasons, primary cutaneous lymphomas were included as distinct entities in recent classifications for malignant lymphomas (EORTC 1997; WHO-EORTC 2005; WHO 2008). Two main categories can be distinguished: primary cutaneous T-cell lymphomas (CTCL), accounting for 75-80% of cases and primary cutaneous B-cell lymphomas (CBCL), accounting for 20-25% of cases. Within the group of CTCLs three subgroups can be distinguished: (1) the group of classical CTCLs, including mycosis fungoides (MF), variants of MF, and Sézary syndrome (SS); (2) the group of primary cutaneous CD30-positive lymphoproliferative disorders (CD30+ LPD); and (3) a group of rare and often aggressive cutaneous T/NK-cell lymphomas. Table 1 shows the WHO-EORTC classification and relative frequencies of most cutaneous lymphomas. The studies in this thesis focused on cutaneous CD30-positive lymphoproliferations, in particular primary cutaneous anaplastic large cell lymphoma (C-ALCL). As C-ALCL is part of the group of primary cutaneous lymphomas.

Table 1. WHO-EORTC classification for cutaneous lymphomas

<table>
<thead>
<tr>
<th>Cutaneous T-cell lymphoma</th>
<th>Frequency (%)</th>
<th>5-yr DSS (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mycosis fungoides (variants)</td>
<td>48</td>
<td>88-100</td>
</tr>
<tr>
<td>Sézary syndrome</td>
<td>3</td>
<td>24</td>
</tr>
<tr>
<td>Primary cutaneous CD30+ lymphoproliferative disorders</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Primary cutaneous anaplastic large cell lymphoma</td>
<td>8</td>
<td>95</td>
</tr>
<tr>
<td>Lymphomatoid papulosis</td>
<td>12</td>
<td>100</td>
</tr>
<tr>
<td>Subcutaneous panniculitis-like T-cell lymphoma</td>
<td>1</td>
<td>82</td>
</tr>
<tr>
<td>Primary cutaneous NK/T-cell lymphoma, nasal type</td>
<td>&lt;1</td>
<td>NR</td>
</tr>
<tr>
<td>Primary cutaneous CD4+ small/medium pleomorphic T-cell lymphoma</td>
<td>2</td>
<td>75</td>
</tr>
<tr>
<td>Primary cutaneous aggressive CD8+ T-cell lymphoma</td>
<td>&lt;1</td>
<td>18</td>
</tr>
<tr>
<td>Primary cutaneous γ/δ T-cell lymphoma</td>
<td>&lt;1</td>
<td>NR</td>
</tr>
<tr>
<td>Primary cutaneous peripheral T-cell lymphoma, not otherwise specified</td>
<td>2</td>
<td>16</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Cutaneous B-cell lymphoma</th>
<th>Frequency (%)</th>
<th>5-yr DSS (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Primary cutaneous marginal zone B-cell lymphoma</td>
<td>7</td>
<td>99</td>
</tr>
<tr>
<td>Primary cutaneous follicle centre lymphoma</td>
<td>11</td>
<td>95</td>
</tr>
<tr>
<td>Primary cutaneous large B-cell lymphoma, leg type</td>
<td>4</td>
<td>55</td>
</tr>
</tbody>
</table>

*Data are based on 1905 patients with a primary cutaneous lymphoma registered by the Dutch and Austrian Cutaneous Lymphoma Groups; NR: not reached; DSS: disease specific survival.
CD30+ LPD, this introductory chapter focuses on the clinical aspects, differential diagnosis and molecular aspects involved in the pathogenesis of this subgroup of CTCL.

CD30

In 1982, Schwab et al. described a new molecule that was initially termed Ki-1 and subsequently designated CD30. CD30 is a 120-kDa transmembrane cytokine receptor of the tumor necrosis factor receptor family, located on chromosome 1p36. Interaction between CD30 and its natural ligand CD30L (CD153, located on chromosome 9q33), which is expressed constitutively by granulocytes, activated T-cells and histiocytes, results in pleiotropic effects depending on cell type, state of differentiation or activation and the presence of other stimuli. The CD30 antibody was first reported to react selectively with Hodgkin and Reed-Sternberg cells in Hodgkin's disease and with scattered activated blast cells in the perifollicular areas in reactive lymph nodes and tonsils. Further studies showed that CD30 was also expressed by highly activated B- and T-cells and by a group of diffuse large cell lymphomas, which generally show a T- or null-cell phenotype and sometimes a B-cell phenotype. Because of constant CD30 expression and frequent anaplastic features, these lymphomas were accepted as a distinct morphologic entity, initially called Ki-1 or CD30-positive (large cell) lymphoma and later anaplastic large cell lymphoma (ALCL). In addition, a primary cutaneous variant was recognized (C-ALCL), and it was found that the large atypical cells in skin biopsies of lymphomatoid papulosis (LyP) also express the CD30 molecule. Because of the overlapping clinical, histological and immunophenotypical features, it was then suggested that C-ALCL and LyP are parts of a spectrum of primary cutaneous CD30+ LPD.

THE GROUP OF PRIMARY CUTANEOUS CD30-POSITIVE LYMPHOPROLIFERATIVE DISORDERS

Primary cutaneous CD30+ LPD represent the second most common subgroup of CTCL, accounting for approximately 25% of all CTCL (Table 2). This group includes C-ALCL, LyP and borderline cases. C-ALCL is composed of large cells with anaplastic, pleomorphic, or immunoblastic cytomorphology and expression of the CD30 molecule by more than 75% of the tumor cells and without clinical evidence or history of MF, or another type of CTCL. LyP is defined as a chronic, recurrent, self-healing papulonecrotic or papulonodular skin disease with histologic features suggestive of a (CD30+) malignant lymphoma. As both disorders show overlapping clinical, histological and immunophenotypical features the clinical appearance and course are used as decisive criteria for the definitive diagnosis and choice of treatment. The main clinical characteristics are summarized in Table 2. The term ‘borderline cases’ was initially used for cases with a discrepancy between the clinical features and the histological appearance. Nowadays it refers to cases in which, despite careful clinicopathologic correlation, a definite distinction between C-ALCL and LyP cannot be made yet. Clinical examination during follow-up generally discloses whether the patient has C-ALCL or LyP.
Clinical features

**Primary cutaneous anaplastic large cell lymphoma**

The median age of C-ALCL patients is around 60 years with a male to female ratio of 2-3:1\(^{15,16}\). Most patients present with solitary or localized nodules or tumors, and sometimes papules, often showing ulceration (Figure 1). Multifocal lesions are seen in about 20% of the patients. In about 40% of the cases, the skin may show partial or complete spontaneous regression.\(^{15}\) Skin relapses occur frequently, but extracutaneous dissemination is uncommon.\(^{15,16}\) Prognosis is usually favorable with a 10-year disease-specific survival of approximately 90%.\(^{15,17}\) Risk factors that predict an unfavorable course, occurring in few patients with C-ALCL, are largely unknown. However, several studies have suggested that age older than 60 years, absence of spontaneous remission, and presentation with multifocal skin lesions may correlate with reduced survival.\(^{15,18-20}\) Moreover, extensive single limb involvement and localization on the head and neck have been associated with a less favorable prognosis.\(^{16,21,22}\) In chapter 2 we investigated the prognostic significance of a large number of parameters including sex, age (≤60 vs. >60 years), extent of disease, site of presentation, and complete spontaneous remission of initial skin lesions in a large group of patients (n=135) with C-ALCL. For extent of disease we used the recently described tNM classification system for primary cutaneous lymphomas other than MF and SS, as proposed by the International Society for Cutaneous Lymphomas (ISCL) and Cutaneous Lymphoma Task Force (CLtF) of the EORTC.\(^{23}\) This classification system is meant to replace the use of the Ann Arbor system, which is the primary means for classifying the extent of disease in patients with non-Hodgkin lymphomas. This, because the Ann Arbor system has a number of shortcomings for lymphomas that arise primarily in extranodal sites such as the skin. For instance, in primary cutaneous lymphomas, the initial stage according to the Ann Arbor system would either be IE (if single skin site) or IVD + (if multiple skin sites), thereby disproportionally or inappropriately placing many patients in the highest stage, resulting in unnecessarily aggressive treatments.\(^{23}\) A major goal of the study described in chapter 2 was to investigate the applicability and prognostic value of this new TNM classification system.

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**Table 2.**

<table>
<thead>
<tr>
<th>Extent skin lesions</th>
<th>C-ALCL</th>
<th>LyP</th>
</tr>
</thead>
<tbody>
<tr>
<td>Solitary/localized</td>
<td></td>
<td></td>
</tr>
<tr>
<td>20% complete</td>
<td></td>
<td></td>
</tr>
<tr>
<td>20% partial</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Generalized</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Spontaneous remission</td>
<td>20% complete</td>
<td>100%</td>
</tr>
<tr>
<td>Staging</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>Therapy</td>
<td>Excision/RT</td>
<td>None (MTX/RT)</td>
</tr>
<tr>
<td>Risk to develop systemic disease at 10 years</td>
<td>16%</td>
<td>4%</td>
</tr>
<tr>
<td>Disease related 10-year-survival</td>
<td>&gt;90%</td>
<td>100%</td>
</tr>
</tbody>
</table>

RT: Radiotherapy; MTX: methotrexate
Lymphomatoid papulosis

LyP generally occurs in adults, but may occur in children as well. The median age is around 45 years with a male to female ratio of 1.5-2.1. Most patients present with generalized papular, papulonecrotic, and/or nodular skin lesions at different stages of development, predominantly on the trunk and limbs (Figure 1). Individual skin lesions disappear within 3-12 weeks, and may leave behind superficial scars. The duration of the disease may vary from several months to more than 40 years. LyP has an excellent prognosis. In up to 20% it may be preceded by, associated with, or followed by another type of malignant (cutaneous) lymphoma, generally MF, (C-)ALCL, or Hodgkin lymphoma. Risk factors that identify patients most likely to develop another type of malignant (cutaneous) lymphoma or extracutaneous disease are not known.

Histologic features

**Primary cutaneous anaplastic large cell lymphoma**

C-ALCL show diffuse nonepidermotropic infiltrates with cohesive sheets of large CD30+ tumor cells (Figure 1). In most cases, the tumor cells have the characteristic morphology of anaplastic cells, with round, oval, or irregularly-shaped nuclei, prominent (eosinophilic) nucleoli, and abundant cytoplasm. Less commonly (20-25%), they have a nonanaplastic (pleomorphic or immunoblastic) appearance. Reactive lymphocytes are often present at the periphery of the lesions. Ulcerating lesions may show a LyP-like (type A) histology with an abundant inflammatory infiltrate of reactive T-cells, histiocytes, eosinophils, neutrophils, and few CD30-positive cells.

**Lymphomatoid papulosis**

The histologic picture of LyP is extremely variable and in part correlates with the age of the biopsied skin lesion. Four histologic subtypes (types A, B, C, and D) have been described. In LyP type A lesions, scattered or small clusters of large, sometimes multinucleated or Reed-Sternberg-like, CD30+ cells are intermingled with numerous inflammatory cells, such as histiocytes, small lymphocytes, neutrophils, and/or eosinophils (Figure 1). LyP type C lesions demonstrate a monotonous population or large clusters of large CD30+ T-cells with relatively few admixed inflammatory cells. LyP type B is uncommon (less than 10%) and is characterized by an epidermotropic infiltrate of small CD4+, CD30- atypical cells with cerebriform nuclei similar to that observed in MF. LyP type D consists of an epidermotropic infiltrate of small- to medium-sized CD8+ and CD30+ atypical lymphoid cells that histologically resembles primary cutaneous aggressive epidermotropic CD8+ cytotoxic T-cell lymphoma. Recognition of the different histologic subtypes of LyP has contributed to a better definition and to a better understanding of the relationship between LyP and other types of CTCL. However, from a clinical point of view, differentiation between these different subtypes is not useful, as they do not differ clinically.

**Immunophenotype**

Except for LyP type B, which are generally CD30 negative, CD30+ LPD show CD30 staining on the cell membrane and in the Golgi region of most of the neoplastic cells. In most cases these neoplastic cells have an activated CD4+ T-cell phenotype with variable loss of CD2, CD5 and/or CD3, and frequent expression of granzyme B, TIA-1 and perforin (cytotoxic
Proteins. Some cases have a CD8+ T-cell phenotype. Most primary cutaneous CD30+ LPD express the cutaneous lymphocyte antigen (CLA), but do not express epithelial membrane antigen (EMA) and anaplastic lymphoma kinase (ALK), indicative of the 2;5 chromosomal translocation or its variants in systemic ALCL. Recent studies have reported on the utility of immunohistochemical markers to differentiate between C-ALCL and LyP, such as BCL2, clusterin, TNF-receptor associated factor 1 (TRAF1) and IFN regulatory factor 4 (IRF4; also known as multiple myeloma antigen 1 or MUM1). The results of these studies are often unconfirmed or conflicting. Chapter 3 evaluates the value of some of these phenotypical markers in a large group of cutaneous CD30+ lymphoproliferations.

Genetic features
Clonally rearranged T-cell receptor genes have been detected in nearly all C-ALCL and approximately 60%-70% of LyP lesions. Identical rearrangements have been demonstrated in LyP lesions and associated lymphomas.
The translocation t(2;5) (p23;q35) resulting in expression of NPM-ALK protein (p80), which is predominantly found in systemic ALCL in children, is not or rarely found in LyP and C-ALCL. Recently, a new translocation involving the IRF4 gene locus has been discovered in 20-25% of C-ALCL cases. In other CTCL this translocation has been rarely found.

The results of recent studies employing array-based comparative genomic hybridization (aCGH) and gene expression profiling are described in the following paragraph.

Etiology and pathogenesis

The mechanisms that are involved in the development of primary cutaneous CD30+ LPD are largely unknown. So far, no causative agent has been identified. Because viral antigens may strongly induce CD30 expression in T-and B-cells, a viral etiology has been suggested. However, studies for an etiologic role of human T-lymphotrophic virus-1, Epstein-Barr virus (EBV) and other herpes viruses, including herpes simplex virus (HSV) type 1 and type 2 and human herpesvirus-6, 7, and 8, have been consistently negative.

Spontaneous remission is one of the most characteristic features of these CD30-positive lymphomas and occurs, by definition, in all patients with LyP and in approximately 40% of cases of C-ALCL. Several studies have investigated the expression of apoptosis related proteins that may contribute to the spontaneous disappearance of skin lesions. For instance, it was shown that the FAS receptor is consistently expressed by CD30+ LPD tumor cells, in contrast to aggressive types of CTCL. In addition, lower levels of the antiapoptotic protein BCL2 were found in LyP compared with nonregressing lesions of C-ALCL suggesting that increased BCL2 expression in nonregressing lesions of C-ALCL protects tumour cells from apoptosis. It was also suggested that interactions between CD30 and CD30L may contribute to apoptosis of the neoplastic T-cells. However, the exact mechanisms responsible for the regression of skin lesions are still unknown. Regarding possible mechanisms for tumor progression, unresponsiveness to the growth inhibitory effects of transforming growth factor-beta (TGF-beta) by point mutations and deletions in the TGF-beta type I and type II receptors, as well as high levels of BCL2 expression by the CD30-positive tumor cells have been suggested.

Recent studies have shed light on molecular (epi)genetic features of C-ALCL. Using aCGH analysis van Kester et al. identified several recurrent copy number alterations including gains on chromosome 7q and 17q and losses on 6q and 13q. Nearly identical results were found in a recent study by Laharanne et al., using a different aCGH platform. In both studies the 9p21 deletion (involving the CDKN2A-CDKN2B gene locus) was rare or absent in C-ALCL patients, which is in contrast to patients with transformed mycosis fungoides (MF-TR). In the same study by van Kester et al. gene expression profiling showed increased expression of skin-homing chemokine receptors compared to cutaneous peripheral T-cell lymphoma, not otherwise specified (PTL-NOS), which may contribute to the lower tendency to disseminate to extracutaneous sites. Additionally, based on the increased expression of CD30, TRAF1 and IRF4 Wozniak and Piris speculate that CD30-mediated NF-kB activation may play a role in the pathogenesis of C-ALCL.

On the epigenetic level van Doorn et al. found that BCL7a was hypermethylated at a lower frequency in C-ALCL (14%) compared to aggressive types of CTCL (64%). They suggested that this gene functions as a tumor suppressor in lymphoid cells. Little is known about histon modifications and miRNA expression in C-ALCL, which next to DNA methylation influence the epigenetic landscape.
Several studies have demonstrated specific miRNA expression profiles in different types of CTCL suggesting a role in the pathogenesis of these disorders. In chapter 5 we investigated the miRNA expression profile of C-ALCL and compared the results with tumor stage MF.

Differential diagnosis

CD30 is not only expressed by the conditions included in the group of primary cutaneous CD30+ LPD, but also by systemic anaplastic large cell lymphoma involving the skin secondarily, MF-TR, certain other lymphomas and reactive skin conditions, which may mimic CD30+ LPD histologically (Table 3).

Secondary cutaneous anaplastic large cell lymphomas

Two types of systemic ALCL are included as separate entities in the WHO 2008 classification: ALK+ and ALK- ALCL. ALK+ ALCL is associated with the t(2;5) translocation resulting in expression of the anaplastic large cell lymphoma kinase (ALK) protein. ALK+ ALCL occur most frequently in the first three decades of life and often involve both lymph nodes and extranodal sites such as skin. It has a relatively good prognosis with a 5-year overall survival of approximately 80%. Extranal sites are less commonly involved in ALK- ALCL, but can include skin as well. Patients with ALK- ALCL have a higher median age than ALK+ ALCL and their survival is significantly worse with an overall 5-year survival rate of only 46%.

In order to differentiate between a primary and secondary cutaneous ALCL adequate staging investigations have to be performed. According to guidelines from the Dutch Cutaneous Lymphoma Group (DCLG), this staging work-up should include physical examination, laboratory studies, imaging studies and a bone marrow biopsy. However, recent data from the registry of the DCLG show that in an increasing number of patients with an ALCL presenting in the skin, in particular those presenting with a solitary tumor that has resolved spontaneously

Table 3. Differential diagnosis of cutaneous CD30+ lymphoproliferations

<table>
<thead>
<tr>
<th>Primary cutaneous CD30+ lymphoproliferative disorders</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Primary cutaneous anaplastic large cell lymphoma</td>
</tr>
<tr>
<td>• Lymphomatoid papulosis</td>
</tr>
<tr>
<td>• Borderline cases</td>
</tr>
</tbody>
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<table>
<thead>
<tr>
<th>Transformed mycosis fungoides</th>
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</table>

<table>
<thead>
<tr>
<th>Systemic ALCL with secondary skin involvement</th>
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</thead>
</table>

<table>
<thead>
<tr>
<th>Other lymphomas</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Other CTCL that sometimes express CD30: epidermotropic CD8+ CTCL, pagetoid reticulosis, patch or plaque stage MF</td>
</tr>
<tr>
<td>• CD30+ cutaneous B-cell lymphomas: e.g. posttransplant (EBV+) LPD, MTX-associated lymphomas</td>
</tr>
<tr>
<td>• Hodgkin lymphoma with secondary skin involvement</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Reactive skin conditions</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Atopic dermatitis</td>
</tr>
<tr>
<td>• Drug reactions</td>
</tr>
<tr>
<td>• Viral infections: Milker’s nodule, HIV, HSV or VZV infections, molluscum contagiosum</td>
</tr>
<tr>
<td>• Persistent arthropod bite reactions</td>
</tr>
<tr>
<td>• Cutaneous lymphoid hyperplasia (pseudolymphoma)</td>
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</table>
or has been excised completely, staging is incomplete and particularly a bone marrow biopsy is not always performed. Moreover, the recently published classification system for non-MF/SS primary cutaneous lymphomas suggests that in cutaneous lymphomas with an indolent clinical behavior such as C-ALCL, bone marrow evaluation should be considered, but is not required, unless indicated by other staging assessments.\(^2\) In **chapter 4** we investigated whether the current policy to advice bone marrow examination in all patients with C-ALCL should be maintained or whether it should be performed only in selected cases.

**Transformed mycosis fungoides**

MF is the most common type of CTCL (Table 1), clinically characterized by the slow progression from patches to plaques and in a proportion of patients to tumors and development of extracutaneous disease.\(^2\) Histologically, the early stages of MF show superficial band-like or lichenoid infiltrates with atypical small- to medium-sized T-cells with highly indented (cerebriform) nuclei into the epidermis (epidermotropism). With progression to tumor stage, the dermal infiltrates become more diffuse, with an increase in the proportion of tumor cells as well as an increase in the number of blast cells, and epidermotropism may get lost. While patients with early patch or plaque stage MF generally run an indolent course with a 10-year DSS over 80%, patients developing skin tumors or extracutaneous disease have a reduced 10-year DSS of 42% and <20%, respectively.\(^5\) Apart from clinical stage, large cell transformation (LCT) has been associated with an aggressive clinical course and a poor survival. LCT is defined by the presence of large T cells exceeding 25% of the total lymphoid infiltrate or forming microscopic nodules. These large T-cells may be CD30+ or CD30-. In view of the excellent prognosis of C-ALCL (CD30+), several studies have evaluated whether CD30 expression in MF-TR is associated with a good survival as well.\(^5,9\) However, in none of the published studies a significant difference between CD30+ and CD30- cases was found, probably because of the small size of the study groups. Evaluation of studies to prognostic factors in MF-TR is further hampered by the inclusion of not only patients with MF but also variable numbers of patients with SS and by variable proportions of patients with LCT at extracutaneous sites. To find out whether CD30 expression and other prognostic factors are related to a better survival of patients with MF-TR, we have evaluated clinicopathologic and immunophenotypical data in a large group of patients. The results are presented in **chapter 6**.

**Other lymphomas**

Other types of cutaneous lymphoma that may express CD30 can be divided in three groups: (1) well-defined types of CTCL that sometimes express the CD30 antigen including CD8-positive epidermotropic CTCL\(^6\), pagetoid reticulosis\(^8\) and rare cases of patch or plaque stage MF; (2) skin localizations of CD30+ B-cell lymphomas, such as (EBV positive) posttransplant LPD or MTX associated lymphoma and (3) classical Hodgkin lymphoma with secondary skin involvement.\(^4\)

**Reactive skin conditions**

Increasing numbers of benign skin conditions are being identified, in which the reactive inflammatory infiltrate may contain scattered or sometimes large clusters of large CD30+ T-cells, which mimic LyP or C-ALCL histologically. These include atopic dermatitis, lymphomatoid drug reactions, viral infections (e.g. Milker’s nodule, human immunodeficiency virus (HIV), HSV or
varicella zoster virus (VZV) infections, molluscum contagiosum), persistent arthropod bite reactions and pseudolymphoma (Table 2).

Treatment

Treatment of CD30+ LPD should primarily be based on the size, the extent, and the clinical behavior of the skin lesions. In LyP, one should take into account that a curative therapy is not available and that none of the available treatment modalities affects the natural course of the disease. For that reason, the short term benefits of active treatment should be balanced carefully against the potential side effects. For patients with few non-scarring lesions active treatment is not necessary. For patients with numerous, disseminated, or stigmatizing lesions, low-dose methotrexate (5-25 mg/week) and phototherapy, in particular PUVA, are preferred options.

Solitary or localized C-ALCL are usually treated with surgical excision or radiotherapy. The preferred type of treatment in patients with multifocal skin lesions has been subject of debate. For a long time, multiagent chemotherapy has been used as first-line therapy in patients with multifocal skin lesions. However, skin relapses are common. In recent EORTC, ISCL and United States Cutaneous Lymphoma Consortium consensus recommendations multiagent chemotherapy is therefore only advised in patients developing extracutaneous disease. For multifocal skin lesions low-dose Methotrexate (5-25 mg/week), as in LyP, is suggested. Alternatively, retinoids or interferon can be considered.

AIM AND OUTLINE OF THE THESIS

The studies presented in this thesis have aimed to address questions regarding clinical aspects, differential diagnosis and molecular aspects involved in the pathogenesis of cutaneous CD30+ lymphoproliferations.

Chapter 2 evaluates the applicability and prognostic value of the new TNM classification system for primary cutaneous lymphomas other than MF and SS in patients with C-ALCL and investigates the prognostic significance of other clinical variables.

Chapter 3 analyses the diagnostic and prognostic value of phenotypic markers TRAF1, MUM1, BCL2 and CD15 in several cutaneous CD30-positive lymphoproliferations including C-ALCL, LyP, CD30+ MF-TR and skin localizations of systemic ALCL.

Chapter 4 evaluates the current policy to advice bone marrow examination to patients with an ALCL presenting in the skin.

Chapter 5 provides an analysis of the miRNA expression profiles of skin biopsies from C-ALCL patients compared to skin biopsies from patients with benign inflammatory dermatoses and tumor stage MF.

Chapter 6 retrospectively analyses prognostic factors in patients with MF-TR and provides a prognostic index.

Chapter 7 summarizes and discusses the findings described in the preceding chapters.
REFERENCES


38. Pham-Ledard A, Prochazkova-Carlotti M, Laharanne E et al. IRF4 gene rearrangements define a subgroup of CD30-positive cutaneous...


General introduction