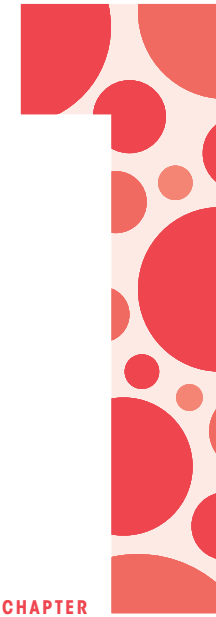
Diagnostic and prognostic markers of cutaneous lymphomas

Schrader, A.M.R.



CHAPTER

GENERAL INTRODUCTION

CUTANEOUS LYMPHOMAS

Primary cutaneous lymphomas are a heterogeneous group of non-Hodgkin lymphomas that present in the skin without evidence of extracutaneous disease at the time of diagnosis.[1] The majority, with 75% to 80%, constitutes of cutaneous T-cell lymphomas (CTCLs), while cutaneous B-cell lymphomas (CBCLs) only comprise 20% to 25% of all cutaneous lymphomas.[1] The different types of CTCLs and CBCLs have distinct clinical and histological characteristics. In addition, the clinical behavior and prognosis is often completely different from the morphologically similar systemic lymphomas that may involve the skin secondarily. Therefore, cutaneous lymphomas require different treatment regimens and are included as distinct entities in the current lymphoma classifications.[2,3]

In the 2018 update of the World Health Organization and European Organization for Research and Treatment of Cancer (WHO-EORTC) classification, 4 main groups of primary cutaneous lymphomas are distinguished: 1) classic types of CTCL, which include mycosis fungoides (MF), MF variants, and Sézary syndrome (SS); 2) primary cutaneous $CD30^+$ lymphoproliferative disorders ($CD30^+$ LPDs), which include primary cutaneous anaplastic large-cell lymphoma (C-ALCL) and lymphomatoid papulosis (LyP); 3) a heterogeneous group of CTCL other than MF, SS, and $CD30^+$ LPDs; and 4) the group of CBCL, which include primary cutaneous follicle center lymphoma (PCFCL), primary cutaneous diffuse large B-cell lymphoma, leg type (PCDLBCL-LT), primary cutaneous marginal zone lymphoma (PCMZL), intravascular large B-cell lymphoma (IVLBCL), and EBV-positive mucocutaneous ulcer. The relative frequency and prognosis of the different types of CTCL and CBCL are presented in Table 1.

This thesis includes several immunophenotypic and molecular studies in different types of cutaneous lymphomas aiming to identify markers that may aid in diagnosis -classification- and prognosis -risk stratification- of patients with cutaneous lymphomas. In this introductory chapter, the main characteristics of these types of cutaneous lymphomas are described. The rare subtypes are listed in Table 2, but these will not be further discussed. In the final chapter of this thesis, the results

of these studies are summarized and reviewed with regard to clinical implications and future perspectives.

Table 1. WHO-EORTC classification 2018 of primary cutaneous lymphomas[1]

	Frequency (%)	5-year DSS (%)
Cutaneous T-cell lymphomas		
Mycosis fungoides	39	88
Variants of mycosis fungoides		
Folliculotropic mycosis fungoides	5	75
Pagetoid reticulosis	<1	100
Granulomatous slack skin	<1	100
Sézary syndrome	2	36
Adult T-cell leukemia/lymphoma	<1	unknown
Primary cutaneous CD30$^+$ lymphoproliferative disorders		
Cutaneous anaplastic large-cell lymphoma	8	95
Lymphomatoid papulosis	12	99
Subcutaneous panniculitis-like T-cell lymphoma	1	87
Extranodal NK/T-cell lymphoma, nasal type	<1	16
Chronic active EBV infection	<1	unknown
Primary cutaneous γ/δ T-cell lymphoma	<1	11
CD8$^+$ aggressive epidermotropic cutaneous T-cell lymphoma*	<1	31
Primary cutaneous CD4$^+$ small/medium T-cell lymphoproliferative disorder*	6	100
Primary cutaneous acral CD8$^+$ T-cell lymphoma*	<1	100
Primary cutaneous peripheral T-cell lymphoma, not otherwise specified	2	15
Cutaneous B-cell lymphomas		
Primary cutaneous follicle center lymphoma	12	95
Primary cutaneous diffuse large B-cell lymphoma, leg type	4	56
Primary cutaneous marginal zone lymphoma	9	99
Intravascular large B-cell lymphoma	<1	72
EBV-positive mucocutaneous ulcer*	<1	100

Abbreviations: WHO, World Health Organization; EORTC, European Organization for Research and Treatment of Cancer; DSS, disease-specific survival; EBV, Epstein-Barr virus.
** Provisional entity*

Table 2. Clinical, histopathological, and immunophenotypic characteristics of rare types of cutaneous T-cell lymphomas

	Clinical features	Histopathology	Immunophenotype
SPTCL	subcutaneous nodules	subcutis infiltrates with rimming around the adipocytes	$CD4^-CD8^+$/ αβ-TCR
PCGD-TCL	ulcerating plaques and tumors	variable infiltration of epidermis, dermis, and/or subcutis	$CD4^-CD8^{+/-}$/ γδ-TCR
$CD8^+$ AETCL	ulcerating plaques, nodules, and tumors	varying from marked pagetoid epidermotropism to deep dermal infiltrates	$CD4^-CD8^+$/ αβ-TCR
PCSM-LPD	solitary nodule or tumor on the face of upper trunk	diffuse or nodular infiltrates of scattered pleiomorphic cells in a mixed background	$CD4^+CD8^-$/ αβ-TCR
PTCL-NOS	cases that do not fit into any of the other, well-defined types of CTCL		

Abbreviations: SPTCL, subcutaneous panniculitis-like T-cell lymphoma; PCGD-TCL, primary cutaneous γ/δ T-cell lymphoma; $CD8^+$ AETCL, $CD8^+$ aggressive epidermotropic cutaneous T-cell lymphoma; PCSM-LPD, primary cutaneous $CD4^+$ small/medium T-cell lymphoproliferative disorder; PTCL-NOS, primary cutaneous peripheral T-cell lymphoma, not otherwise specified.

Cutaneous T-cell lymphomas

Mycosis fungoides

MF is the most common type of CTCL, comprising almost 40% of all cutaneous lymphomas and nearly 50% if also the variants of MF are taken into account.[1] Patients with classical MF present with erythematous, scaly patches and plaques, and may develop tumors in more advanced disease stages (Figure 1A). Skin lesions can arise in all body sites, but are preferentially located at non-sun-exposed areas such as the gluteal region. The skin lesions are asymptomatic and slowly progress over years or decades.[2] Skin biopsies characteristically show epidermotropic infiltration by medium-sized, atypical lymphocytes with a cleaved "cerebriform" morphology, often aligning along the basement membrane (Figure 2A). The neoplastic lymphocytes may show an aberrant T-cell immunophenotype with variable loss of the pan-T-cell markers CD2, CD3, CD5, and CD7. Usually, the neoplastic lymphocytes have a $CD4^+CD8^-$ phenotype, but also $CD4^-CD8^+$ or even 'double positive' and 'double negative' phenotypes exist.[4] In early-stage disease, the superficial dermis shows a sparse, band-like infiltrate with a low number

of neoplastic cells and a variable amount of admixed inflammatory cells. In advanced-stage disease, the dermal infiltration of tumor cells becomes more dense and may extend into the deep dermis or subcutaneous tissue. Epidermotropism may no longer be present. The tumor cells may progress into cells with a blastic morphology with a larger size and a prominent nucleolus. This process is also referred to as "large-cell transformation".[5] Treatment of MF mainly consists of skin-directed therapies, such as topical corticosteroids and photo(chemo)therapy. In case of tumor-stage disease, local radiotherapy can be given, and in case of widespread disease and/or extracutaneous disease, polychemotherapy, whether or not followed by allogeneic stem cell transplantation, is indicated.[6] Prognosis of patients with MF depends on the disease stage, with an excellent 5-year survival of 95% in early disease, but a poor 5-year survival of 52% in patients with advanced, tumor-stage disease.[7,8] In addition, large-cell transformation is associated with an inferior survival.[8]

Sézary syndrome

SS is a rare subtype of CTCL that is defined by the triad of pruritic erythroderma (redness of ≥75% of the skin; Figure 1B), generalized lymphadenopathy, and the presence of clonally-related neoplastic T cells with cerebriform nuclei (Sézary cells) in the skin, lymph nodes, and peripheral blood.[1] As both the clinical and histopathological presentation may be non-specific, demonstration of peripheral blood involvement is essential for diagnosis of SS. The criteria for blood involvement include identification of the same clone in the skin and the peripheral blood in combination with either an absolute Sézary cell-count of >1000/μL, or an expanded $CD4^+$ T-cell population resulting in a CD4:CD8 ratio of ≥ 10, $CD4^+/CD7^-$ cells in ≥ 40%, or $CD4^+/CD26^-$ cells in ≥ 30%.[2,3] Histologically, SS is highly similar to MF. Features that favor SS over MF are sparser superficial infiltrates, minimal presence or absence of epidermotropism, and, if present, clustering of the epidermotropic cells into so called Pautrier's micoabcesses (Figure 2B), instead of showing alignment along the basement membrane, as is more characteristic for MF.[1] Treatment of SS consists of systemic therapies, such as low-dose methotrexate, interferon-α, extracorporeal photophoresis, and, more recently, targeted molecular therapies.[6] Patients with SS have a poor prognosis with a 5-year disease-specific survival (DSS) of only 36%.[1]

In early stages, the clinical presentation as well as the histologic features of MF and SS can be very subtle. Therefore, it is not uncommon that cases are misdiagnosed as atopic dermatitis or other benign inflammatory dermatoses (BIDs). Misdiagnosis often results in a diagnostic delay. To improve differentiation between MF/SS and BIDs, more specific and sensitive markers in daily clinical practice are needed. Previously, Zhang et al.[9] performed gene-expression profiling and compared the expression profiles of early-stage MF with healthy skin and BIDs. One of the differentially expressed proteins was thymocyte-selection high mobility group box (TOX), which showed a high potential as discriminative marker for early-stage MF compared with BIDs. TOX is normally upregulated during specific phases of the development of T cells in the thymus, but is not expressed in mature T cells that circulate though the body. Several later studies confirmed the findings by Zhang et al. and demonstrated aberrant expression of TOX by the $CD4^+CD8^-$ neoplastic cells of MF and SS.[10-16] However, little is known about expression of TOX in MF with other than the $CD4^+CD8^-$ phenotype and in other subtypes of CTCL. *Therefore, in **chapter 2** of this thesis, the clinical utility of TOX protein expression is studied in a large group of patients with several subtypes of CTCL with different phenotypes and compared with the expression of TOX in BIDs.*

In this study, we unexpectedly noticed expression of TOX in follicular areas of reactive lymph nodes and tonsils that were used as external controls. *This prompted us to further study TOX expression in various types of CBCL. The results of this study are presented in **chapter 3**.*

Primary cutaneous $CD30^+$ lymphoproliferative disorders

Primary cutaneous $CD30^+$ LPDs account for 20% of all primary cutaneous lymphomas.[1] $CD30^+$ LPDs are a disease spectrum with C-ALCL on one side and LyP on the other side (Table 3). Clinically, C-ALCL presents as solitary, grouped or, uncommonly, multifocal nodules and tumors (Figure 1C).[1] LyP, on the other hand, is characterized by “waxing and waning” of multiple, self-healing, erythematous papules that can manifest all over the body (Figure 1D). Characteristically, these papules are present in different phases of development, ranging from very early ‘fresh’ lesions to fully regressed lesions that only leave post-inflammatory

hyperpigmentation or hypopigmentation. The common histopathologic feature is dermal infiltration of large, anaplastic T cells with strong expression of the marker CD30 (Figure 2C-D). In addition, the tumor cells show variable to extensive marker loss, often only retaining the cytotoxic markers TIA1 and/or Granzyme B. Distinction between C-ALCL and LyP is based on the clinical presentation and clinical course, and cannot be done on histopathology alone. As LyP has a very characteristic clinical presentation and excellent prognosis, treatment is usually not required. In case of cosmetically-disturbing lesions, such as scarring or presence of numerous papulonodules, low-dose oral methotrexate may reduce the number of skin lesions.[17] In C-ALCL, staging at time of diagnosis is required to exclude secondary skin involvement of systemic ALCL. The preferred treatment of C-ALCL is low-dose radiotherapy.[18] Survival of patients with primary cutaneous CD30$^+$ LPDs is usually excellent, with a 5-year DSS of 95% for patients with C-ALCL and 99% for patients with LyP.[19,20] However, rare cases develop progressive disease with extracutaneous dissemination and may even die from their lymphoma.[20] Currently, it is not possible to identify these patients at an early disease stage.

Table 3. Differential features of cutaneous anaplastic large-cell lymphoma and lymphomatoid papulosis

	C-ALCL	**LyP**
Skin lesions	(solitary) tumors	(multiple) papules
Spontaneous remission	40%	100%
Staging	yes	no
Treatment	RT (excision)	expectative (MTX/RT)
Extracutaneous dissemination	12%	3%
Disease-specific survival at 5 years	95%	99%

Abbreviations: C-ALCL, cutaneous anaplastic large-cell lymphoma; LyP, lymphomatoid papulosis; RT, radiotherapy; MTX, methotrexate.

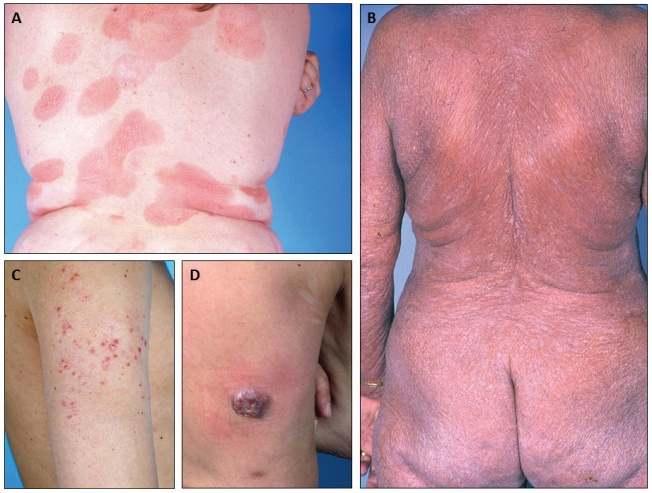


Figure 1. Representative clinical presentation of (A) early-stage mycosis fungoides with erythematous, scaly patches on the trunk, (B) Sézary syndrome with erythroderma, (C) lymphomatoid papulosis with erythematous papules on the upper arm, and (D) primary cutaneous anaplastic large-cell lymphoma with a solitary, ulcerating tumor on the back.

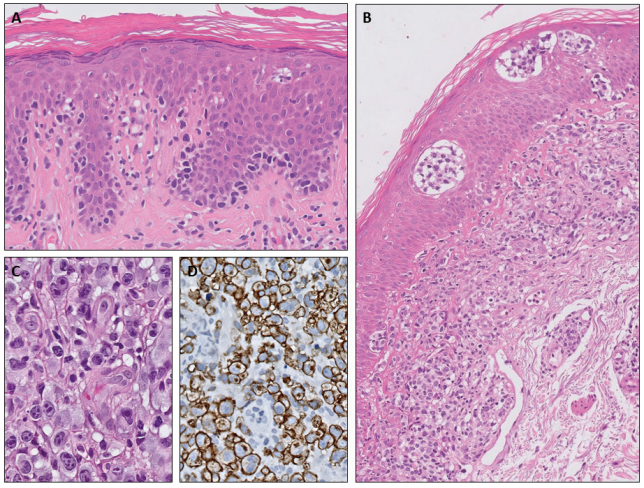


Figure 2. Representative histopathology of (A) early-stage mycosis fungoides with epidermotropism of atypical lymphocytes that align along the basement membrane, (B) Sézary syndrome with Pautriers microabcesses, and (C) primary cutaneous anaplastic large-cell lymphoma with diffuse dermal infiltration of large, anaplastic cells that (D) show strong expression of CD30.

In systemic ALCL, several recurrent chromosomal rearrangements have been described that are associated with the disease course of the patients. Approximately half of the patients harbor *ALK* rearrangements and these patients have a superior 5-year overall survival (80%) compared with patients without an *ALK* rearrangement (50%).[21] Within the group of ALK$^-$ ALCL patients, mutually exclusive rearrangements in *DUSP22* and *TP63* were detected in 30% and 8% of the patients, respectively.[21,22] Patients with *DUSP22* rearrangements demonstrate a similar survival as ALK$^+$ patients, while patients harboring *TP63* rearrangements have the worst prognosis with a 5-year overall survival of only 17%.[21-23] In primary cutaneous CD30$^+$ LPDs, *ALK* rearrangements are usually absent.[24] *DUSP22* rearrangements are detected in 30% of the C-ALCL patients and rarely in LyP patients, but are without clinical significance.[24-26] So far, *TP63* rearrangements have only been detected in 5% of the C-ALCL patients and not in LyP patients.[23,27] Despite the overall excellent prognoses of primary cutaneous CD30$^+$ LPDs, a small subset of patients with C-ALCL and LyP shows disease progression. Therefore, we wondered whether these patients might also harbor *TP63* rearrangements. *In **chapter 4**, the presence of TP63 rearrangements was investigated in patients with C-ALCL and LyP that were selected for an aggressive disease course.*

Cutaneous B-cell lymphomas

In contrast to the more frequent CTCL, only 4 subtypes and 1 provisional entity of CBCLs are recognized by the WHO-EORTC classification for cutaneous lymphomas.[1] The 3 subtypes with a large cell morphology will be discussed of which PCFCL and PCDLBCL-LT may share common features and can be difficult to distinguish (Table 4).

Primary cutaneous follicle center lymphoma

PCFCL is the most common type of CBCL and represents 12% of all cutaneous lymphomas.[1] Clinically, patients with PCFCL present with localized skin lesions on the head and/or trunk (Figure 3A). These lesions are histologically composed of small to large, cleaved cells (named centrocytes) with a variable amount of admixed centroblasts (Figure 4A).[28,29] In some instances, the tumor cells are spindle-shaped.[30] PCFCL may present with either a follicular, a follicular and diffuse, or a diffuse growth pattern.[2] The immunophenotype of PCFCL is that of a germinal center B-cell,

with expression of BCL6 and sometimes CD10, while BCL2 and MUM1 are mostly negative.[31] The preferred treatment of PCFCL is local radiotherapy. Response to initial treatment is excellent, with a complete remission rate of 99%.[31] Despite this high rate of complete remission, patients commonly develop cutaneous relapses (30%). Extracutaneous dissemination, on the other hand, is rare and occurs in <10% of the patients with PCFCL and survival is excellent with a 5-year DSS of 95%.[31,32]

Table 4. Differential features of primary cutaneous diffuse large B-cell lymphoma, leg type and primary cutaneous follicle center lymphoma

	PCDLBCL-LT	**PCFCL**
Skin lesions	tumor(s) on the legs; other sites uncommon	localized lesions on the head and trunk; other sites uncommon
Morphology of tumor cells	immunoblasts and/or centroblasts	centrocytes; variable amount of centroblasts
Growth pattern	diffuse	follicular; follicular and diffuse; diffuse
Admixed T cells	sparse	abundant
(Remnants of) FDC networks	no	yes
Immunophenotype	$BCL2^+$/ $MUM1^+$/ IgM^+	$BCL6^+$ / $BCL2^-$ / $MUM1^-$ / IgM^-
Molecular profile	NF-κB-activating mutations	No NF-κB-activating mutations
Treatment	R-CHOP	RT
Extracutaneous dissemination	50%	10%
Disease-specific survival at 5 years	56%	95%

Abbreviations: PCDLBCL-LT, primary cutaneous diffuse large B-cell lymphoma, leg type; PCFCL, primary cutaneous follicle center lymphoma; FDC, follicular dendritic cell; ABC, activated B-cell; GCB, germinal center B-cell; R-CHOP, rituximab plus cyclophosphamide, doxorubicin, vincristine, and prednisone; RT, radiotherapy.

Primary cutaneous diffuse large B-cell lymphoma, leg type

PCDLBCL-LT is the most aggressive CBCL and comprises 4% of all cutaneous lymphomas.[1] The disease usually affects older, female patients with a median age of disease onset of ~70 years. Patients present with purple to bluish tumors on the legs, as the name implies, although also other sites of the skin can be affected (Figure 3B).[2] To exclude secondary cutaneous involvement of systemic diffuse

large B-cell lymphoma (DLBCL), staging procedures should be performed, at least consisting of a PET-CT scan or a CT-scan in combination with a bone marrow biopsy. Skin biopsies of PCDLBCL-LT show a diffuse infiltration of the dermis by blastic B cells with a predominance of large, non-cleaved cells (centroblasts and/or immunoblasts) (Figure 4B). Admixture of small, reactive T cells is often sparse.[31] The tumor cells have a B-cell phenotype, positive for CD20, CD79A, and PAX5, and almost always concurrently express the activated B-cell markers BCL2, MUM1, and IgM.[31] Standard treatment of PCDLBCL-LT consists of immuno-polychemotherapy (a combination of rituximab plus cyclophosphamide, doxorubicin, vincristine, and prednisone; R-CHOP) or, in case of a solitary lesion and poor clinical condition of the patient, of radiotherapy.[1] As in PCFCL, response to initial treatment is usually excellent with a complete remission rate of 85% for PCDLBCL-LT.[31] However, cutaneous relapses and extracutaneous dissemination occur frequently, with percentages of up to 70% and 50%, respectively.[31] The 5-year DSS of patients with PCDLBCL-LT is only 56%.[1] Currently, no routine classifiers are available to predict which patients will have a more aggressive disease course with relapsed/refractory disease.

In systemic DLBCL, cases with concurrent rearrangements of the *MYC* and *BCL2* and/or *BCL6* genes are separately classified as "high-grade B-cell lymphomas" because of their aggressive behavior.[33] In addition, double protein expression of MYC and BCL2 was shown to negatively influence prognosis of systemic DLBCL patients, although not as severely as the cases with double (or triple) rearrangement status.[34-36] In the cutaneous large B-cell lymphomas, the presence of these chromosomal rearrangements and protein expression has only been studied in few cases and the prognostic significance is unknown. *Therefore, in **chapter 5**, the frequency and prognostic significance of MYC rearrangements, with or without a double hit in BCL2 and/or BCL6, and double protein expression of MYC and BCL2 was evaluated in patients with PCDLBCL-LT and PCFCL.*

Besides chromosomal rearrangements in *MYC*, *BCL2*, and/or *BCL6*, several highly frequent mutations may occur in PCDLBCL-LT, such as in *MYD88* and *CD79B*.[37-40] These mutations are supposed drivers of the disease; however, little is known about the molecular profile during disease evolution and about molecular alterations

that may affect the prognosis of the patients. *For this reason, in **chapter 6**, the mutational profile of a relatively large cohort of patients with PCDLBCL-LT was studied at diagnosis and at relapse and correlated with survival outcome of the patients.*

Intravascular large B-cell lymphoma

One of the rarest subtypes of CBCL is the intravascular large B-cell lymphoma (IVLBCL). IVLBCL usually presents as systemic disease with involvement of multiple organs, but can also present in the skin as the only site of involvement at time of diagnosis (the "cutaneous variant").[41] Skin lesions commonly consist of purple to bluish plaques or diffuse telangiectasias (Figure 3C-D). Other commonly affected organs are the central nervous system and the lungs. The cutaneous variant is present in ~25% of the, mostly female, patients.[41] As the name implies, this type of lymphoma is characterized by exclusive or predominant growth of neoplastic B cells in the lumen of blood vessels and capillaries (Figure 4C).[3] The exact mechanism of the tumor cells to remain restricted to the blood vessels is unknown, but a defect in the homing receptors, such as integrin β1 and ICAM1 adhesion molecules, was proposed.[42] The tumor cells of IVLBCL are B cells that commonly express BCL2 and MUM1, similar to the immunophenotype of PCDLBCL-LT.[31,43] In addition, a subset of cases aberrantly co-expresses the T-cell marker CD5.[43] Standard treatment of patients with an IVLBCL is with R-CHOP.[44] Overall survival of patients with the cutaneous variant is 72% at 3 years, and these patients were shown to have a superior survival compared with patients with the systemic variant of IVLBCL.[41] Therefore, it is important to identify the presence or absence of systemic lesions at time of diagnosis. As IVLBCL is a rare disease, so far, little is known about the molecular alterations that drive lymphomagenesis. *Therefore, we were prompted to investigate the genetic alterations in patients with cutaneous and systemic variants of an IVLBCL. The results of these studies are presented in **chapter 7**.*

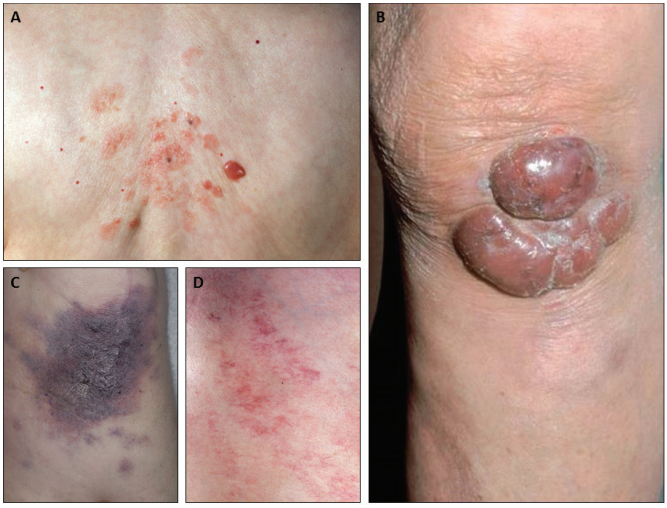


Figure 3. Representative clinical presentation of (A) primary cutaneous follicle center lymphoma with localized, erythematous tumors and plaques on the trunk, (B) primary cutaneous diffuse large B-cell lymphoma, leg type with tumors on the knee, and intravascular large B-cell lymphoma with (C) bluish, indurated plaques and (D) generalized telangiectasias.

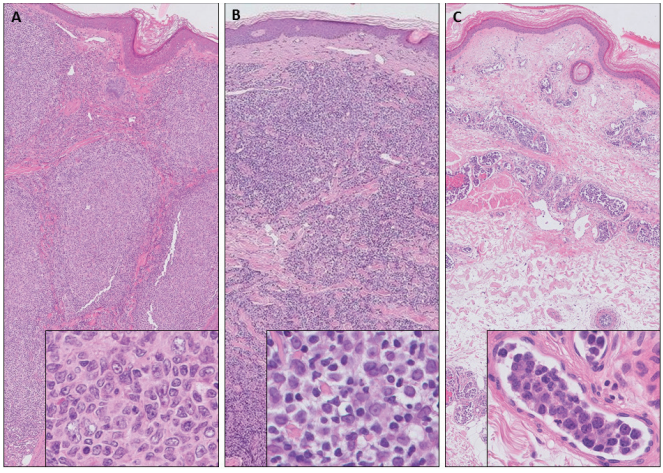


Figure 4. Representative histopathology of (A) primary cutaneous follicle center lymphoma with a follicular growth pattern, composed of medium to large, cleaved cells, (B) primary cutaneous diffuse large B-cell lymphoma, leg type with diffuse dermal infiltration of large, non-cleaved cells, and (C) intravascular large B-cell lymphoma with intravascular localization of large, non-cleaved cells.

REFERENCES

1. Willemze R, Cerroni L, Kempf W, et al. The 2018 update of the WHO-EORTC classification for primary cutaneous lymphomas. *Blood*. 2019;133(16):1703-1714.
2. Elder DE ed WHO Classification of Skin Tumours. In: Massi DS, RA; Willemze, R ed (ed 4th). Lyon: IARC; 2018.
3. Swerdlow SH ed WHO Classification of Tumours of Haematopoietic and Lymphoid Tissues. In: Campo ELH, N; Jaffe, ES; Pileri, SA; Stein, H; Thiele, J; Vardiman, JW ed (ed Revised 4th). Lyon: IARC; 2017.
4. Massone C, Crisman G, Kerl H, Cerroni L. The prognosis of early mycosis fungoides is not influenced by phenotype and T-cell clonality. *Br J Dermatol*. 2008;159(4):881-886.
5. Dmitrovsky E, Matthews MJ, Bunn PA, et al. Cytologic transformation in cutaneous T cell lymphoma: a clinicopathologic entity associated with poor prognosis. *J Clin Oncol*. 1987;5(2):208-215.
6. Trautinger F, Eder J, Assaf C, et al. European Organisation for Research and Treatment of Cancer consensus recommendations for the treatment of mycosis fungoides/ Sezary syndrome - Update 2017. *Eur J Cancer*. 2017;77:57-74.
7. Scarisbrick JJ, Prince HM, Vermeer MH, et al. Cutaneous Lymphoma International Consortium Study of Outcome in Advanced Stages of Mycosis Fungoides and Sezary Syndrome: Effect of Specific Prognostic Markers on Survival and Development of a Prognostic Model. *J Clin Oncol*. 2015;33(32):3766-3773.
8. Agar NS, Wedgeworth E, Crichton S, et al. Survival outcomes and prognostic factors in mycosis fungoides/Sezary syndrome: validation of the revised International Society for Cutaneous Lymphomas/European Organisation for Research and Treatment of Cancer staging proposal. *J Clin Oncol*. 2010;28(31):4730-4739.
9. Zhang Y, Wang Y, Yu R, et al. Molecular markers of early-stage mycosis fungoides. *J Invest Dermatol*. 2012;132(6):1698-1706.
10. Huang Y, Litvinov IV, Wang Y, et al. Thymocyte selection-associated high mobility group box gene (TOX) is aberrantly over-expressed in mycosis fungoides and correlates with poor prognosis. *Oncotarget*. 2014;5(12):4418-4425.
11. Huang Y, Su MW, Jiang X, Zhou Y. Evidence of an oncogenic role of aberrant TOX activation in cutaneous T-cell lymphoma. *Blood*. 2015;125(9):1435-1443.
12. Yu X, Luo Y, Liu J, Liu Y, Sun Q. TOX acts an oncological role in mycosis fungoides. *PLoS One*. 2015;10(3):e0117479.
13. Morimura S, Sugaya M, Suga H, et al. TOX expression in different subtypes of cutaneous lymphoma. *Arch Dermatol Res*. 2014;306(9):843-849.

14. Litvinov IV, Netchiporouk E, Cordeiro B, et al. The Use of Transcriptional Profiling to Improve Personalized Diagnosis and Management of Cutaneous T-cell Lymphoma (CTCL). *Clin Cancer Res*. 2015;21(12):2820-2829.

15. Boonk SE, Cetinozman F, Vermeer MH, Jansen PM, Willemze R. Differential expression of TOX by skin-infiltrating T cells in Sezary syndrome and erythrodermic dermatitis. *J Cutan Pathol*. 2015;42(9):604-609.

16. McGirt LY, Adams CM, Baerenwald DA, Zwerner JP, Zic JA, Eischen CM. miR-223 regulates cell growth and targets proto-oncogenes in mycosis fungoides/cutaneous T-cell lymphoma. *J Invest Dermatol*. 2014;134(4):1101-1107.

17. Bruijn MS, Horvath B, van Voorst Vader PC, Willemze R, Vermeer MH. Recommendations for treatment of lymphomatoid papulosis with methotrexate: a report from the Dutch Cutaneous Lymphoma Group. *Br J Dermatol*. 2015;173(5):1319-1322.

18. Melchers RC, Willemze R, Bekkenk MW, et al. Evaluation of treatment results in multifocal primary cutaneous anaplastic large cell lymphoma: report of the Dutch Cutaneous Lymphoma Group. *Br J Dermatol*. 2018;179(3):724-731.

19. Bekkenk MW, Geelen FA, van Voorst Vader PC, et al. 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. *Blood*. 2000;95(12):3653-3661.

20. Melchers RC, Willemze R, Vermaat JSP, et al. Outcomes of rare patients with a primary cutaneous CD30+ lymphoproliferative disorder developing extracutaneous disease. *Blood*. 2020;135(10):769-773.

21. Parrilla Castellar ER, Jaffe ES, Said JW, et al. ALK-negative anaplastic large cell lymphoma is a genetically heterogeneous disease with widely disparate clinical outcomes. *Blood*. 2014;124(9):1473-1480.

22. King RL, Dao LN, McPhail ED, et al. Morphologic Features of ALK-negative Anaplastic Large Cell Lymphomas With DUSP22 Rearrangements. *Am J Surg Pathol*. 2016;40(1):36-43.

23. Vasmatzis G, Johnson SH, Knudson RA, et al. Genome-wide analysis reveals recurrent structural abnormalities of TP63 and other p53-related genes in peripheral T-cell lymphomas. *Blood*. 2012;120(11):2280-2289.

24. Xing X, Feldman AL. Anaplastic large cell lymphomas: ALK positive, ALK negative, and primary cutaneous. *Adv Anat Pathol*. 2015;22(1):29-49.

25. Pham-Ledard A, Prochazkova-Carlotti M, Laharanne E, et al. IRF4 gene rearrangements define a subgroup of CD30-positive cutaneous T-cell lymphoma: a study of 54 cases. *J Invest Dermatol*. 2010;130(3):816-825.

26. Wada DA, Law ME, Hsi ED, et al. Specificity of IRF4 translocations for primary cutaneous anaplastic large cell lymphoma: a multicenter study of 204 skin biopsies. *Mod Pathol*. 2011;24(4):596-605.

27. Chavan RN, Bridges AG, Knudson RA, et al. Somatic rearrangement of the TP63 gene preceding development of mycosis fungoides with aggressive clinical course. *Blood Cancer J*. 2014;4:e253.

28. Vermeer MH, Geelen FA, van Haselen CW, et al. Primary cutaneous large B-cell lymphomas of the legs. A distinct type of cutaneous B-cell lymphoma with an intermediate prognosis. Dutch Cutaneous Lymphoma Working Group. *Arch Dermatol*. 1996;132(11):1304-1308.

29. Willemze R, Kerl H, Sterry W, et al. EORTC classification for primary cutaneous lymphomas: a proposal from the Cutaneous Lymphoma Study Group of the European Organization for Research and Treatment of Cancer. *Blood*. 1997;90(1):354-371.

30. Oschlies I, Kohler CW, Szczepanowski M, et al. Spindle-Cell Variants of Primary Cutaneous Follicle Center B-Cell Lymphomas Are Germinal Center B-Cell Lymphomas by Gene Expression Profiling Using a Formalin-Fixed Paraffin-Embedded Specimen. *J Invest Dermatol*. 2017;137(11):2450-2453.

31. Senff NJ, Hoefnagel JJ, Jansen PM, et al. Reclassification of 300 primary cutaneous B-Cell lymphomas according to the new WHO-EORTC classification for cutaneous lymphomas: comparison with previous classifications and identification of prognostic markers. *J Clin Oncol*. 2007;25(12):1581-1587.

32. Willemze R, Jaffe ES, Burg G, et al. WHO-EORTC classification for cutaneous lymphomas. *Blood*. 2005;105(10):3768-3785.

33. Swerdlow SH, Campo E, Pileri SA, et al. The 2016 revision of the World Health Organization classification of lymphoid neoplasms. *Blood*. 2016;127(20):2375-2390.

34. Hu S, Xu-Monette ZY, Tzankov A, et al. MYC/BCL2 protein coexpression contributes to the inferior survival of activated B-cell subtype of diffuse large B-cell lymphoma and demonstrates high-risk gene expression signatures: a report from The International DLBCL Rituximab-CHOP Consortium Program. *Blood*. 2013;121(20):4021-4031; quiz 4250.

35. Green TM, Young KH, Visco C, et al. Immunohistochemical double-hit score is a strong predictor of outcome in patients with diffuse large B-cell lymphoma treated with rituximab plus cyclophosphamide, doxorubicin, vincristine, and prednisone. *J Clin Oncol*. 2012;30(28):3460-3467.

36. Rosenthal A, Younes A. High grade B-cell lymphoma with rearrangements of MYC and BCL2 and/or BCL6: Double hit and triple hit lymphomas and double expressing lymphoma. *Blood Rev*. 2017;31(2):37-42.

37. Mareschal S, Pham-Ledard A, Viailly PJ, et al. Identification of somatic mutations in primary cutaneous diffuse large B-cell lymphoma, leg-type by massive parallel sequencing. *J Invest Dermatol*. 2017;137:1984-1994.

38. Koens L, Zoutman WH, Ngarmlertsirichai P, et al. Nuclear factor-kappaB pathway-activating gene aberrancies in primary cutaneous large B-cell lymphoma, leg type. *J Invest Dermatol*. 2014;134(1):290-292.

39. Pham-Ledard A, Beylot-Barry M, Barbe C, et al. High frequency and clinical prognostic value of MYD88 L265P mutation in primary cutaneous diffuse large B-cell lymphoma, leg-type. *JAMA Dermatol*. 2014;150(11):1173-1179.

40. Zhou XA, Louissaint A, Jr., Wenzel A, et al. Genomic Analyses Identify Recurrent Alterations in Immune Evasion Genes in Diffuse Large B-Cell Lymphoma, Leg Type. *J Invest Dermatol*. 2018;138(11):2365-2376.

41. Ferreri AJ, Campo E, Seymour JF, et al. Intravascular lymphoma: clinical presentation, natural history, management and prognostic factors in a series of 38 cases, with special emphasis on the 'cutaneous variant'. *Br J Haematol*. 2004;127(2):173-183.

42. Ponzoni M, Arrigoni G, Gould VE, et al. Lack of CD 29 (beta1 integrin) and CD 54 (ICAM-1) adhesion molecules in intravascular lymphomatosis. *Hum Pathol*. 2000;31(2):220-226.

43. Murase T, Yamaguchi M, Suzuki R, et al. Intravascular large B-cell lymphoma (IVLBCL): a clinicopathologic study of 96 cases with special reference to the immunophenotypic heterogeneity of CD5. *Blood*. 2007;109(2):478-485.

44. Ferreri AJ, Dognini GP, Bairey O, et al. The addition of rituximab to anthracycline-based chemotherapy significantly improves outcome in 'Western' patients with intravascular large B-cell lymphoma. *Br J Haematol*. 2008;143(2):253-257.