Pathologic Diagnosis of Cutaneous Lymphomas

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KEYWORDS

• Lymphoma • Lymphoproliferative • Cutaneous • Skin • Diagnosis • Clinicopathological correlation • T cell • B cell

KEY POINTS

- Clinicopathologic correlation is an essential element in the diagnostic approach to cutaneous lymphomas.
- Cutaneous lymphomas show overlapping histologic and immunophenotypic features, but can differ significantly in their course and prognosis.
- Monoclonality does not necessarily indicate malignancy. Lack of monoclonality does not exclude the diagnosis of cutaneous lymphoma.

INTRODUCTION

Primary cutaneous lymphomas (CLs) comprise a heterogeneous group of lymphocytic neoplasms with a broad spectrum of clinical, histologic, immunophenotypical, and genetic features (**Box 1**).[1–3] The histopathological examination plays an essential role and is often the starting point in the diagnostic workup of CLs. The classification of CLs follows the current World Health Organization (WHO) classification (4th edition, 2008), which is widely accepted by hematopathologists and dermatopathologists.[3] The WHO classification of the tumors of hematopoietic and lymphoid tissues follows the multiparameter approach by defining lymphomas according to their clinical, histopathological, immunophenotypic, and genetic features as well as the side of primary manifestation, which was originally introduced by the Revised European-American Lymphoma classification (REAL).[4,5]

This aim of this review is to provide an approach based on the growth patterns, cytomorphology, phenotypic, and genetic features for primary CLs and to emphasize the impact of clinicopathological correlation.

Pathologic Approach

Histopathologically, various *growth patterns* can be distinguished. Some are more prevalent in certain forms of CLs, whereas others are found throughout the entire spectrum of CLs. The growth patterns and cytomorphology provide first diagnostic hints. For example, epidermotropic infiltrates of small to medium-sized lymphocytes are most commonly found in cutaneous T-cell lymphomas (CTCLs), whereas dense dermal lymphocytic infiltrates, of variable size and cytomorphology, are commonly present in cutaneous B-cell lymphomas (CBCLs).

For practical reasons, 6 major patterns can be distinguished in CLs: epidermotropic, nodular, diffuse, subcutaneous, angiocentric/angiodestructive, and intravascular. Among each growth pattern, additional histopathological features may

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Box 1
World Health Organization classification for lymphoid neoplasms

MATURE T-CELL AND NK-CELL NEOPLASMS

Mycosis fungoides (MF)

MF variants and subtypes:

Folliculotropic MF

Pagetoid reticulosis

Granulomatous slack skin

Sézary syndrome

Adult T-cell leukemia/lymphoma

Primary cutaneous CD30+ T-cell lymphoproliferative disorders

Primary cutaneous anaplastic large cell lymphoma

Lymphomatoid papulosis

Subcutaneous panniculitis-like T-cell lymphoma

Extranodal NK-/T-cell lymphoma, nasal type

Primary cutaneous peripheral T-cell lymphoma

Rare subtypes:

- Primary cutaneous CD8+ aggressive epidermotropic cytotoxic T-cell lymphoma (provisional)
- Primary cutaneous γ/δ T-cell lymphoma
- Primary cutaneous CD4+ small/medium T-cell lymphoma (provisional entity)

Primary cutaneous peripheral T-cell lymphoma, unspecified

MATURE B-CELL NEOPLASMS

Extranodal marginal zone lymphoma of mucosa-associated lymphoid tissue (MALT lymphoma)

Primary cutaneous follicle center lymphoma

Diffuse large B-cell lymphoma, NOS

Primary cutaneous diffuse large B-cell lymphoma, leg type

Primary cutaneous diffuse large B-cell lymphoma, others

Intravascular large B-cell lymphoma

Note: This list is mainly limited to cutaneous lymphomas in the WHO classification.

Data from Swerdlow SH, Campo E, Harris NL, et al. WHO classification of tumours of haematopoietic and lymphoid tissues. 4th edition. Lyon (France): IARC Press; 2008.

be identified, such as folliculotropic and syringotropic infiltrates or granulomatous features.

- Epidermotropic infiltrates are most commonly found in CTCLs, particularly in their initial disease stage (eg, mycosis fungoides [MF], patch, and plaque stage), throughout the entire disease evolution like in Sézary syndrome (SS), or in cutaneous $CD8^+$ aggressive epidermotropic cytotoxic T-cell lymphoma (AETCL).
- Nodular and diffuse infiltrates are a hallmark of progressive forms of CTCLs (eg, MF tumor stage; peripheral T-cell lymphoma [PTCL] unspecified) as well as CBCLs.
- The subcutaneous growth pattern is typically found in subcutaneous lymphomas, including the subcutaneous panniculitis-like T-cell lymphoma (SPTCL) with expression of T-cell receptor (TCR) α/β and the subcutaneous form of γ/δ T-cell lymphoma, but may rarely be observed as rare variants in other CTCL and CBCL forms.
- Angiocentric and angiodestructive (ie, angioinvasive) infiltrates are characteristic for aggressive T- and T-/natural killer (NK)-cell lymphomas, such as extranodal T-/NK-cell lymphoma, nasal type, and cutaneous γ/δ T-cell lymphoma. Exceptions to the rule are indolent or low-malignant forms of CD30+ T-cell lymphoproliferations as lymphomatoid

papulosis (LyP) type E and the angioinvasive variant of primary cutaneous anaplastic large-cell lymphoma (PCALCL).
- The intravascular growth pattern is pathognomonic for intravascular T- and B-cell lymphoma.

Cytomorphologically, small, medium-sized, and large lymphocytes can be distinguished with variable degrees of nuclear pleomorphism. In B-cell lymphomas, small lymphocytes with lymphoplasmacytoid differentiation, monozytoid B cells, as well as tumor cells with centrocyte-like differentiation can be distinguished from tumor cells resembling centroblast, immunoblasts, and plasmablasts. Noteworthy, an immunoblastic differentiation can also be seen in some form of CTCLs, especially in PCALCL, MF tumor stage, and cutaneous PTCLs, unspecified.

Phenotyping

Immunohistochemistry allows assigning the tumor cells to distinct subsets of T, B, NK/T, or NK cells, including their functional subsets (eg, follicular helper T cells or regulatory T cells). For some forms of CLs, the phenotypic features represent essential diagnostic criteria. For example, in SPTCLs, by definition, the tumor cells require expression of the α/β chain of the TCR. Certain phenotypic and genetic markers not only are of diagnostic importance but also have a prognostic implication (eg, loss of 9p21 in diffuse large B-cell lymphoma, leg-type) or represent therapeutic targets (eg, CD30, anaplastic lymphoma kinase [ALK]/p80). These markers should be specifically mentioned in the pathology report.

Genotyping

CLs are considered to represent monoclonal proliferation of T or B cells displaying identical rearrangement of TCR genes or the genes of the heavy chain of immunoglobulins (IgH). Therefore, clonality assays are mostly based on polymerase chain reaction (PCR) or Southern blot analysis, which can serve as an adjunctive diagnostic marker for CLs. It has, however, to be emphasized that the detection of a clonal T- or B-cell population by itself per se is not proving the diagnosis of lymphoma, because clonal lymphocyte populations can also be found in a subset of inflammatory skin disorders like eczematous reactions or lichenoid skin disorders.[6] Apart from clonality assays, additional genetic analysis allows the identification of genetic alterations, which are characteristic for certain CL entities.

Almost all phenotypic and genetic analyses can nowadays be examined on archival (ie, formalin-fixed and paraffin-embedded) tissue. Because a detailed characterization of a lymphocytic infiltrate requires analyzing several phenotypic factors and, in many cases, also genetic alterations and clonality studies, biopsies or excisions of sufficient size are mandatory. In practical terms, a punch biopsy of 4 to 6 mm diameter or ideally a spindle-shaped excision with an axis length of 1 cm should be taken and immediately transferred to buffered 10% formalin at room temperature. Considering the rapid evolution of new and emerging prognostic and therapeutic markers, a tissue bank is recommended in which access to archived tissue is preserved: additional fresh tissue can be stored in liquid nitrogen at $-80^{\circ}C$ or transferred to special fixatives that preserve RNA, DNA, and proteins for future examinations.

In most cases, the histopathological and the phenotypic analyses alone are limited to provide a list of differential diagnoses. As outlined earlier, CLs display overlapping clinical, histologic, immunophenotypic, and genetic features. As a consequence, clinicopathological correlation is of utmost importance to achieve the final diagnosis. Thereby, the terminology should follow the nomenclature of CLs as given in the current WHO classification for hematopoietic and lymphoid tissues to facilitate communication between clinicians and pathologists.[3]

In the following, the diagnostic criteria, the differential diagnoses, and the impact of immunophenotypical and genetic analysis for the diagnostic workup are discussed in an entity-based approach.

CUTANEOUS T-CELL LYMPHOMAS

Mycosis Fungoides

This CTCL accounts for approximately 40% to 50% of all CLs and represents therefore the most common form. The WHO classification defines the disease by its classical presentation with an evolution of 3 stages: patches, plaques, and tumors.[1–3] The disease shows a broad spectrum of clinical, histologic, and phenotypic variants. Some of these variants do not clinically follow the classic presentation with patches, plaques, and tumors, but rather exhibit unusual features such as the papular variant of MF. The papular variant, which can also be found in follicular MF and other rare clinical variants, has not been considered in the current WHO classification.

Histology

The histologic findings in early MF are subtle, and therefore, histologic diagnosis is challenging. There is a perivascular infiltrate in the upper

dermis, which contains mostly small lymphocytes, eosinophils, and a few plasma cells. The lymphocytes show subtle nuclear atypia and may be arranged along the junctional zone (lining-up) and single-cell epidermotropism (**Fig. 1**). Occasionally, vacuolization along the junctional zone can be seen. Pautrier microabscesses, which are a hallmark of plaque stage, are found in less than 20% of the cases in the patch stage.[7] In MF plaque stage, a denser bandlike infiltrate in the upper and middermis with a prominent epidermotropism of small to medium-sized atypical lymphocytes with nuclear pleomorphism and formation of Pautrier microabscesses is usually found. MF tumor stage is characterized by a dense dermal infiltrate extending into the upper parts of the subcutis, which is composed of pleomorphic tumor cells of variable size. Thereby, transformation is defined by the presence of at least 25% of large tumor cells. Usually an admixture of eosinophils, plasma cells, and histiocytes can be seen. Ulceration commonly occurs. The epidermotropism of tumor cells, as is seen in patch and plaque stage of MF, can get lost in tumor stage of the disease.

Immunophenotype and clonality

Various phenotypes can be observed in MF with a $CD4^+$- T-helper phenotype being the most common one. Other phenotypes include $CD8^+$, $CD30^+$, $CD56^+$, as well as CD4/CD8-double-positive or CD4/CD8 double-negative variants.[8,9] None of these phenotypes were shown to have a prognostic impact in MF patch or plaque stage.[10] However, cases of early MF with CD30 expression in early disease stage and a high proliferation rate particularly in the dermal component of the infiltrate have been found to be more aggressive in one study.[11] Loss of markers, particularly CD7, can be observed in MF, but also in inflammatory dermatosis. Expression of CD7 by less than 10% of the lymphocytes was proposed as a diagnostic criterion for early MF.[12] Nevertheless, the loss of this marker has little diagnostic impact, because expression of CD7 by less than 10% of the infiltrating lymphocytes is a rare finding. In addition, an increased CD4:CD8 ratio (more than 8:1) may be a hint for MF. Recently, the expression of thymocyte selection associated HMG-box (TOX) was found in a high number of early MF lesions by immunohistochemistry, but is rarely observed in chronic dermatosis.[13] Thus, this marker may be useful in the distinction, but further studies are needed to confirm this observation. Some phenotypes are more commonly associated with unusual clinical features such as $CD8^+$ MF, which often presents with hyperpigmented or hypopigmented patches and plaques, whereas CD4/CD8 double-negative phenotype may be associated with annular lesions.[14,15]

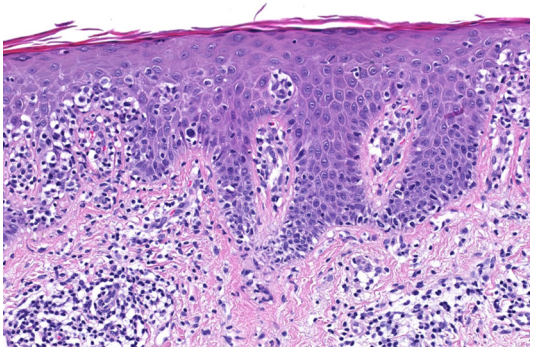

Fig. 1. MF, patch stage: epidermotropism of atypical lymphocytes. HE, ×100.

In tumor stage, loss of T-cell markers may occur and variable expression of CD30 can be seen. Expression of CD30 in tumor stage was shown to be an independent marker for a better disease-related survival.[16] The expression of programmed cell death 1 (PD-1) can occur in all stages of MF and is not a helpful marker in the differentiation from other forms of CLs.

Because monoclonal rearrangement of TCR genes can only be found in half of the early MF cases, clonality studies are of limited value in the diagnosis of early MF.

Genetics

Inactivation of the CDKN2A-CDKN2B was shown to be associated with shorter survival in patients with transformed MF demonstrating deletion of this locus.[17]

Differential diagnosis

The history and the clinicopathologic correlation are essential to distinguish early MF from chronic eczema, psoriasis, actinic reticulosis, as well as so-called lymphomatoid drug eruptions and lymphomatoid contact dermatitis. Among lymphomas, early MF needs to be distinguished from LyP (type B and D), epidermotropic forms of cutaneous γ/δ T-cell lymphoma, SS, and adult T-cell lymphoma/leukemia (ATLL). The differential diagnosis includes, depending on the cell size of the tumor cells, a primary cutaneous CD4-positive small/medium-sized T-cell lymphoma ($CD4^+$- SMTL), which, however, clinically usually presents with a solitary nodule and not with patches and plaques as MF. Moreover, epidermotropism is only focally present or entirely absent in $CD4^+$- SMTL. The distinction of MF tumor stage from PCALCL may be impossible in individual cases on histologic grounds alone. Recently, the expression of

5-hydroxymethylcytosine (5-hMC) was shown to be a useful marker in the distinction. However, the most important differentiation criterion is the presence of patches and plaques preceding the evolution of tumors in MF, whereas PCALCL presents with rapidly growing solitary or grouped nodules without preceding patches and plaques.

Variants

Particularly, MF variants linked to an impaired prognosis deserve special attention. Those variants include the follicular (synonym folliculotropic) as well as the granulomatous form of the disease. Follicular (synonym folliculotropic) MF is characterized by a perifollicular dense infiltrate of mostly small to medium-sized atypical lymphocytes with prominent folliculotropism (**Fig. 2**). Epidermotropism into the interfollicular epidermis, which is a useful diagnostic finding for MF, is absent in 40% to 60% of folliculotropic MF.[18] The latter may be accompanied by mucinous degeneration of the hair follicle epithelia in half of the cases. Distinction from idiopathic follicular mucinosis is challenging. The detection of significant nuclear atypia, an elevated CD4/CD8 ratio, the presence of numerous $CD30^+$- cells, and monoclonal rearrangement of TCR genes as well as the clinical features with multiple alopecic patches and patches or papular lesions indicate MF, whereas the occurrence of a solitary lesion in a young patient, particularly in children, and lack of nuclear atypia argue for idiopathic follicular mucinosis.[19] In addition, other forms of CTCLs such as follicular LyP and ATLL, which can manifest with folliculotropic infiltrates and accompanying follicular mucinosis, have to be distinguished from folliculotropic MF.[20,21] Folliculotropic MF and granulomatous MF carry an impaired prognosis of approximately 60% to 70% 5-year survival rate.[22,23] Therefore, the recognition and intense therapy are essential.

Remarkably, the presence of a syringotropic component, which may accompany folliculotropic infiltrates or occur exclusively without a folliculotropic component, does not show an impaired prognosis compared with the classic type of MF.[24]

The granulomatous variant of MF presents in most cases with sarcoid-like granulomas, occasionally with granuloma anulare-like features (**Fig. 3**).[25,26] The nuclear atypia of the mostly small lymphocytes is rather subtle. In addition, epidermotropism is absent in half of the cases. Distinction from sarcoidosis and other granulomatous diseases is challenging and often results in a delay in diagnosing granulomatous MF. Detection of clonal T cells is a useful adjunctive diagnostic marker to separate granulomatous MF from sarcoidosis.[27,28]

Pagetoid reticulosis is a rare unilesional MF subtype presenting with a solitary psoriasiform or hyperkeratotic lesion often at acral sites.[29] Histologically, a prominent epidermotropism and nuclear pleomorphism of the epidermotropic atypical lymphocytes are seen. Various phenotypes have been identified in pagetoid reticulosis. Therefore, the differential diagnosis is broad and includes $CD4^+$, $CD8^+$, $CD30^+$, as well as $CD56^+$ epidermotropic infiltrates. Pagetoid reticulosis shows the same excellent prognosis as other forms of unilesional MF.[30]

Sézary Syndrome

This rare CTCL form accounts for 2% to 3% of all CLs. SS carries the phenotype of central memory T cells, whereas MF phenotypically corresponds to effector memory T cells.[31] Because the histologic features are nonspecific in up to 40% of the biopsies, the characteristic clinical presentation

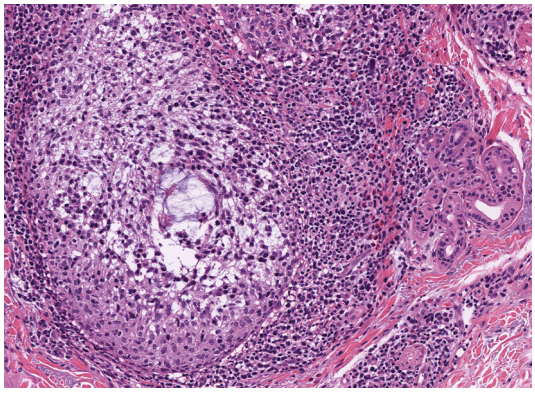

Fig. 2. Follicular MF: folliculotropic infiltrates of small to medium-sized lymphocytes with nuclear atypia. Note mucinous degeneration of the hair follicle epithelium (follicular mucinosis). HE, ×200.

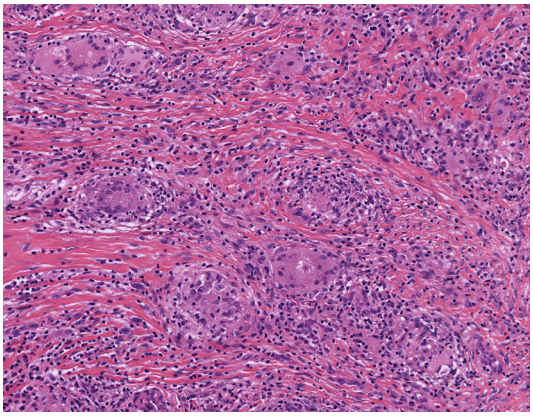

Fig. 3. Granulomatous MF: sarcoidlike granulomas with admixture of small lymphocytes with subtle nuclear atypia. HE, ×100.

with erythroderma, palmoplantar hyperkeratosis, enlarged lymph nodes, and particularly, the detection of more than a thousand cerebriform large tumor cells per milliliter in the peripheral blood are crucial for the diagnosis of SS. In addition, the detection of an identical TCR clone in the skin and the peripheral blood is a useful criterion.

Despite classic MF and SS representing different lymphomas, the histologic features are very similar between SS and MF patch and plaque stage. SS is histologically characterized in many cases by a dense bandlike monotonous lymphocytic infiltrate of small lymphocytes with nuclear atypia (**Fig. 4**). The infiltrate appears more monotonous than in MF. Eosinophils and plasma cells can be admixed. Epidermotropism with formation of Pautrier microabscesses is found in about 60% of the cases, but can be completely absent. Moreover, a pretreatment with topical steroids or ultraviolet light may result in the absence of epidermotropic T cells. Repeated biopsies are useful to enhance the diagnostic accuracy.[32,33] Phenotypically, the tumor cells express CD3, CD4, and often PD-1.[34] However, as outlined earlier, PD-1 does not allow distinguishing SS from other forms of CTCL. The distinction from other CTCL forms presenting with erythroderma such as erythrodermic MF and adult T-cell lymphoma/leukemia requires a history with patches and plaques in MF and the detection of human T-lymphotropic virus type 1 (HTLV1)-DNA integrated into the host genome or serologic demonstration of HTLV1 infection in ATLL, respectively. The distinction of SS from erythrodermic inflammatory dissases (EID) is based on histology only achieved with certainty in less than 60% of the cases.[35] The clinicopathologic correlation and the absence of more than 1000 atypical circulating T cells in the peripheral blood per microliter are essential to differentiate an SS from an EID such as atopic dermatitis, psoriasis, pityriasis rubra pilaris, and in particular, erythrodermic drug eruption.

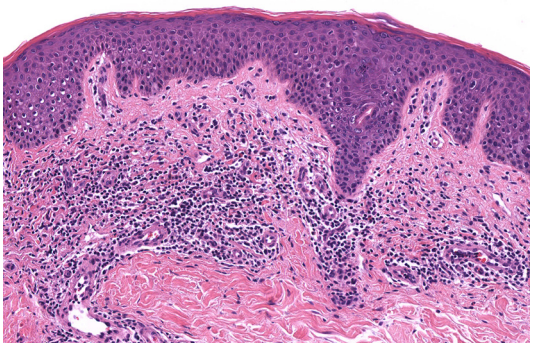

Fig. 4. SS: perivascular monotonous lymphocytic infiltrate in the upper dermis. Note absence of epidermotropism in this biopsy. HE, ×100.

For the distinction of SS and EID, the expression of CD7, PD-1, and TOX may be helpful. PD-1 was expressed by more than 50% of the T cells in 16 of 24 (66%) SS cases, but only in 4 of 30 (13%) EID cases.[34] Although loss of CD7 has been observed in SS as well as in EID, the expression of CD7 by 20% or less of the T cells in skin biopsies was limited to SS. Recent data indicate that the expression of TOX may be an additional marker if more than 50% of the infiltrating T cells show a strong expression of TOX in SS, whereas most cases of EID show only focal and weak expression of this marker.

Primary Cutaneous CD30-Positive Lymphoproliferative Disorders

Primary cutaneous CD30-positive lymphoproliferative disorders represent approximately 20% to 25% of CTCL and comprise a spectrum of lymphoproliferations including LyP and PCALCL as well as so-called borderline lesions.[1,36] The common hallmark of these disorders is the expression of CD30, a tumor necrosis factor superfamily chemokine receptor, by the atypical lymphoid cells.

Lymphomatoid Papulosis

LyP is defined by its characteristic clinical presentation with recurrent papules and small nodules, which undergo spontaneous regression within a few weeks to months. Occasionally, varioliform scars are left behind after regression. The disease has an excellent prognosis without mortality, but patients with LyP are at risk to develop a second lymphoid neoplasm, especially MF, nodal Hodgkin lymphoma, and PCALCL or systemic anaplastic large cell lymphoma (ALCL), before the onset of LyP or during the disease course.

Histology

LyP displays a broad spectrum of histologic manifestations. Five major histologic types can be distinguished (**Table 1**)[37,38]: They differ in regard to the growth pattern (epidermotropic, nodular, angioinvasive), the composition of infiltrate (scattered atypical large CD30+ cells scattered and arranged in small clusters vs cohesive sheets), and the admixture of reactive cells such as neutrophils, eosinophils, and histiocytes. In all histologic types, the atypical lymphocytes express T-cell markers and CD30 except for the histologic type B, characterized by an epidermotropic T-cell infiltrate, which displays variable expression of CD30 (0%–77%) by the small to medium-sized lymphocytes (**Fig. 5**). In addition to these histologic types A to E, a follicular, a granulomatous, and a syringotropic variant of LyP have been described.

Table 1
Lymphomatoid papulosis: histologic types and differential diagnosis

LyP Type	Histology	Differential Diagnosis	Distinguishing Criteria
Type A	Wedge-shaped infiltrate Scattered or in small clusters arranged large CD30+ lymphocytes with nuclear pleomorphism and mitotic activity	• Hodgkin lymphoma (primary or secondary cutaneous)	Staging examination (in nodal HL)
	Background infiltrate of histiocytes, eosinophils, neutrophils	• MF (transformation)	Patches and plaques in MF vs self-regressing papulonodular lesions in LyP
Type B	Epidermotropic infiltrate of small to medium-sized lymphocytes with atypical chromatin-dense nuclei and variable expression of CD30 (0%–77%)	• MF (patch/plaque stage)	Patches and plaques in MF vs self-regressing papulonodular lesions in LyP
		• Cutaneous γ/δ lymphoma (epidermotropic)	Multiple plaques with erosions IHC: Expression of TCR γ
Type C	Nodular cohesive infiltrate of large CD30 + pleomorphic or anaplastic lymphocytes with abundant cytoplasm and mitotic activity	• Anaplastic large-cell lymphoma (primary cutaneous or systemic form)	Clinical presentation with solitary or grouped nodules in PCALCL. Staging examinations in sALCL.
	Admixture of only few eosinophils and neutrophils	• MF (transformation)	Patches and plaques preceding tumors in MF
		• PTCL, NOS (primary cutaneous or nodal)	Lack of CD30 or expression by only a minority of tumor cells, staging examinations
		• Adult T-cell lymphoma/ leukemia	Integration of HTLV-1/2 in tumor cell genome
Type D	Epidermotropism of atypical small to medium-sized pleomorphic lymphocytes with expression of CD8 and CD30	• Pagetoid reticulosis	Unilesional erythematous scaling lesion in pagetoid reticulosis
	Deep dermal or subcutaneous perivascular infiltrates may be present	• Primary cutaneous aggressive epidermotropic CD8+ cytotoxic T-cell lymphoma	Multiple rapidly evolving plaques and nodules with erosions and necrosis Lack of CD30 expression
		• Cutaneous γ/δ lymphoma	Multiple plaques with erosions IHC: Expression of TCR γ
Type E	Angioinvasive (ie, angiocentric and angiodestructive) infiltrates of mostly small to medium-sized pleomorphic CD30+ lymphocytes and expression of CD8+ in 70% of the cases. Admixture of eosinophils.	• Extranodal NK-/T-cell lymphoma, nasal type	Association with EBV, mostly secondary cutaneous involvement (staging)
	Vascular occlusion by atypical lymphocytes or thrombi, hemorrhage, extensive necrosis, and ulceration.	• Cutaneous γ/δ lymphoma	IHC: Expression of TCR γ
		• Anaplastic large-cell lymphoma (primary cutaneous or systemic form) with angiocentric and angiodestructive growth	Clinical presentation with solitary or grouped nodules in PCALCL. Staging examinations in sALCL.

Abbreviations: HL, hodgkin lymphoma; HTLV-1/2, human T-lymphotropic virus type 1/2; IHC, immunohistochemistry; sALCL, systemic anaplastic large-cell lymphoma.

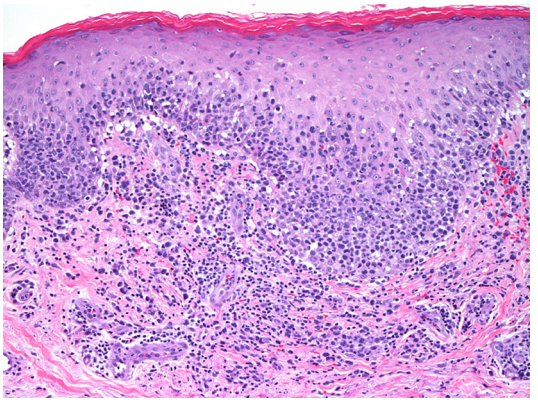

Fig. 5. LyP: epidermotropic infiltrates of small to medium-sized lymphocytes in type B. HE, ×100.

Furthermore, recent genetic studies revealed the presence of IRF4/DUSPP rearrangements on chromosome 6p25.3 in a subset of LyP, which histologically presents with typical histologic findings (ie, an epidermotropic component of atypical small lymphocytes) and, in addition, a dense dermal nodular infiltrate of medium-sized to large atypical $CD30^+$ lymphocytes.[39]

Differential diagnosis

Each of the histologic types of LyP has its differential diagnoses (see **Table 1**). Several infectious and inflammatory skin disorders have been shown to occasionally harbor medium-sized to large $CD30^+$ activated lymphocytes and thus may resemble LyP type A. Detection of clusters of atypical $CD30^+$ cells, the detection of a T-cell clone, and the characteristic clinical presentation allow distinguishing these disorders from LyP type A in most cases.[40,41] LyP type B has to be differentiated from MF, especially because CD30 expression by the epidermotropic lymphocytes can be absent in LyP type B and, on the other hand, MF may show expression of CD30 by epidermotropic lymphocytes even in early disease stage. The clinical presentation, however, allows differentiation between MF (patches, plaques) and LyP (papules and small nodules). A combination of both features within the same lesion has been referred to as persistent agminated LyP. LyP type C resembles the findings in primary cutaneous or systemic ALCL as well as transformed MF. The distinction of those disorders has to rely on clinicopathologic correlation demonstrating patches and plaques in MF and rapidly growing solitary or grouped tumors in ALCL, in contrast to LyP presenting with recurrent papules and small nodules. The distinction of LyP type D from primary cutaneous $CD8^+$ AETCL relies on the clinical presentation with rapidly evolving erosive and ulcerated patches, plaques, and nodules in the latter (**Table 2**).[42] Moreover, expression of CD30 has not been observed in $CD8^+$ AETCL. The distinction of LyP type D from pityriasis lichenoides et variolaformis acuta (PLEVA) with expression of CD8 and CD30 by the intraepidermal cells may be very challenging in individual cases, especially because clinicopathologic correlation does not allow distinguishing the 2 disorders in all patients. LyP type E needs to be distinguished from the angioinvasive form of ALCL as well as from aggressive T-cell lymphomas with angiodestructive and angioinvasive growth, such as extranodal NK T-cell lymphoma and nasal type, by the presence of Epstein-Barr virus (EBV) in the latter and cutaneous γ/δ T-cell lymphoma by the clinical presentation as well as the expression of TCR γ or δ[43] (**Table 3**).

Table 2
CD8-positive epidermotropic infiltrates

MF, $CD8^+$ phenotype	Hypopigmented and hyperpigmented patches/plaques, lining-up, and exocytosis of small lymphocytes with nuclear atypia; CD45R0, $CD30^{+/-}$, T-cell clone[1]
$CD8^+$ AETCL	Rapidly evolving erosive or ulcerated patches, plaques, and nodules. Epidermotropism of small to medium-sized atypical lymphocytes, apoptotic keratinocytes; $CD45RA^+$, $CD30^-$
LyP type D	Recurrent papules and small nodules with spontaneous regression. Epidermotropism of small to medium-sized atypical lymphocytes; $CD8^+$ (100%), $CD30^+$ (90%).
Drug eruption	Maculopapular rash, activated lymphocytes with subtle nuclear atypia; $CD8^+$, $CD30^-$
Pityriasis lichenoides	Papular rash with collerette-like desquamation, vacuolization in the junctional zone, exocytosis of small lymphocytes, apoptotic keratinocytes, focal hyperparakeratosis with inclusion of neutrophils; $CD4^+$ or $CD8^+$, $CD30^{-/+}$

Note: Clonal T cells may also be detected in pityriasis lichenoides (up to 60%) and drug eruption. Thus, detection of a clonal T-cell population is not a useful marker to differentiate between the listed disorders.

Primary Cutaneous Anaplastic Large T-Cell Lymphoma

In most patients, PCALCL presents with rapidly growing solitary or grouped and often ulcerated tumors (**Fig. 6**). Histologically, in the vast majority of the cases, a dense nodular cohesive infiltrate of large pleomorphic, anaplastic, or immunoblastic T cells is found (**Fig. 7**). Morphologic variants include neutrophil-rich, histiocyte-rich, and sarcomatoid and angioinvasive forms (**Fig. 8**).[44–46] Neutrophil-rich PCALCL is more commonly seen in immunocompromised patients. By definition, more than 75% of the cells express CD30. Remarkably, often a weak expression of CD3 or the absence of CD3 expression can be seen. Various phenotypes have been identified with $CD4^+$ T-helper phenotype being the most common one. The phenotype does not have a prognostic impact. In contrast to nodal or systemic ALCL, almost all cases of PCALCL are negative for ALK1 and the underlying translocation t(2;5).[47] Nevertheless, rare cases of ALK-positive PCALCL have been documented.[48] Recently, genetic analysis revealed the presence of IRF4/DUSP22 rearrangements on chromosome 6p25.3 in approximately a third of PCALCL, but not in systemic ALCL. The detection of this translocation by fluorescence in situ hybridization (FISH) represents a useful method in the diagnostic workup of ALCL.[49] It must, however, be emphasized that certain cases of LyP may carry the same rearrangement, and thus, IRF4/DUSP22 rearrangement is not specific for PCALCL. Differential diagnosis includes LyP type C, which can be only distinguished with certainty by clinicopathologic correlation and tumor stage of MF, which occasionally shows expression of CD30 by most tumor cells. The clinicopathologic correlation with patches and plaques in MF patients allows distinction from PCALCL.

Table 3
Angiocentric and angiodestructive (angioinvasive) lymphocytic infiltrates

Extranodal NK-/T-cell lymphoma, nasal type	Ulcerated plaques and nodules Dermal and subcutaneous infiltrates of medium-sized atypical lymphocytes; $CD3\varepsilon^+$ $CD56^+$, $CD30^{-/+}$, $EBER^+$
Cutaneous γ/δ T-cell lymphoma	Erosive or ulcerated plaques and nodules. Dermal and subcutaneous, occasionally epidermotropic infiltrates of atypical lymphocytes with variable size; $CD3^+$ $CD56^+$, $CD30^{-/+}$, $EBER^-$
PTCL, unspecified	Plaques or nodules Dermal and occasionally subcutaneous infiltrates of variably sized atypical lymphocytes $CD3^-$, $EBER^-$
LyP type E (angioinvasive type)	Recurrent papules and small nodules evolving to ulcers (1–4 cm) with spontaneous regression Dermal and occasionally subcutaneous infiltrates of medium-sized lymphocytes $CD3^+$, $CD8^+$ (70%), $CD30^+$ (100%)
Primary cutaneous anaplastic large-cell lymphoma, angioinvasive type	Solitary or grouped tumors with ulceration. Histology and phenotype identical to LyP type E.

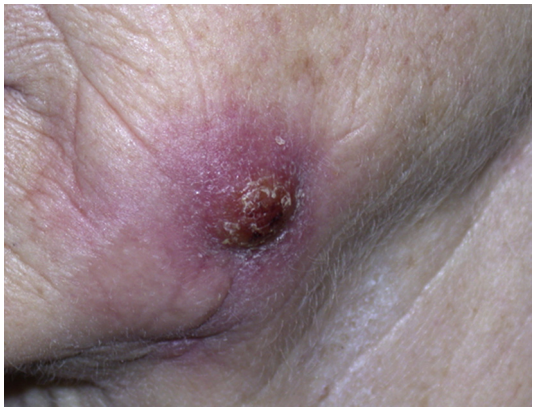

Fig. 6. PCALCL: ulcerated tumor on the left cheek.

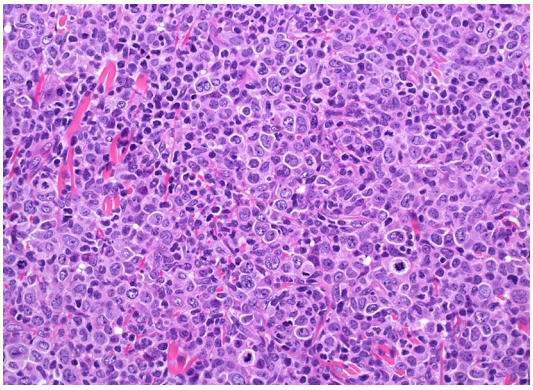

Fig. 7. PCALCL: dense cohesive sheets of anaplastic lymphoid cells. Note mitotic activity. HE, ×200.

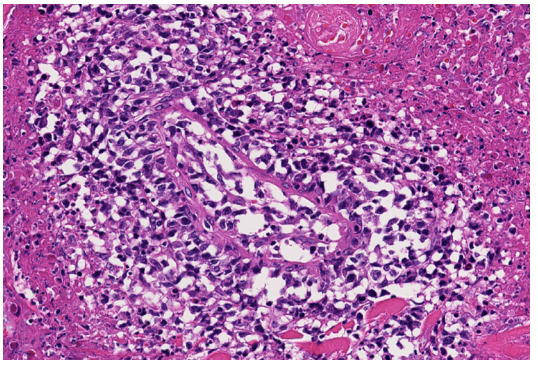

Fig. 8. PCALCL: angioinvasive form with angiocentric and angiodestructive infiltrates of medium-sized to large tumor cells permeating the vessel wall. HE, ×200.

Subcutaneous Panniculitis-Like T-Cell Lymphoma

Despite the fact that SPTCL is a rare lymphoma and accounts for only 1% of all CLs, it represents the vast majority of all subcutaneous forms of T-cell lymphomas (75%). According to the WHO classification, SPTCL is by definition restricted to cases expressing a TCR α/β phenotype.[1,3] Therefore, the immunohistochemical demonstration of the expression of TCR α/β (ie, positivity for β-F1) is the essential diagnostic marker for this entity.

Histology

SPTCL is characterized by a predominantly lobular lymphocytic infiltrate composed of small to medium-sized tumor cells with nuclear pleomorphism.[50] The tumor cells surround lipocytes (so-called rimming). One has to be aware that the rimming of lipocytes, however, is not disease-specific and can be observed in other forms of subcutaneous lymphomas and inflammatory disorders, such as lupus panniculitis. Karyorrhexis and cytophagocytosis may be observed.

Immunophenotype and clonality

Tumor cells in SPTCL express $CD3^+$, $CD4^-$, $CD8^+$, $CD56^-$, TIA 1^+, granzyme B^+, and as the most important marker, β-$F1^+$. There is no association with epstein-barr virus (EBV) infection. Clonal T cells are found in up to 80% of the cases.

Differential diagnosis

Immunophenotyping is essential to differentiate SPTCL from a subcutaneous form of γ/δ T-cell lymphoma, which expresses the γ/δ chain of TCR. The latter can be demonstrated on archival tissue by immunohistochemical detection of TCR γ or on frozen tissue by immunohistochemical detection of TCR δ. In addition, subcutaneous γ/δ lymphoma expresses CD56. In contrast to extranodal T-/NK-cell lymphoma, which may also present with subcutaneous involvement, subcutaneous γ/δ T-cell lymphoma is not associated with EBV. In extranodal T-/NK-cell lymphoma, however, EBV-encoded small RNAs (EBER) can be demonstrated by in situ hybridization. Among nonlymphomatous infiltrates, lupus panniculitis is the major differential diagnosis of SPTCL. Both entities show overlapping histologic features with predominantly lobular lymphocytic infiltrates. In both entities, plasma cells can be observed.[51,52] Useful histopathological criteria for distinguishing lupus panniculitis from SPLTCL include epidermal changes, lymphoid follicles with reactive germinal centers, clusters of B cells, and mixed cell infiltrate with prominent plasma cells in lupus panniculitis.[53] In addition, clusters of $CD123^+$ plasmacytoid dendritic cells are found in lupus panniculitis. Nevertheless, the distinction can be impossible in individual cases. Some authors have suggested that both entities may belong to a spectrum of disease, because lupus panniculitis and SPTCL may occur in the same individual. Furthermore, borreliosis manifesting with lobular panniculitis represents a diagnostic pitfall, because the high number of $CD8^+$ lymphocytes mimics SPTCL, and the plasma cells as well as mucin deposition and clusters of $CD123^+$ plasmacytoid dendritic cells are similar to that seen in lupus panniculitis.[54]

Cutaneous Peripheral T-Cell Lymphoma

PTCL comprise a group of rare subtypes including primary cutaneous $CD4^+$ small/medium-sized lymphoma, primary cutaneous $CD8^+$ aggressive epidermotropic T-cell lymphoma, as well as cutaneous γ/δ T-cell lymphoma. For those cases that do not fit into one of these rare subtypes or any other well-defined CTCL entity, the term cutaneous PTCL unspecified (PTCL NOS) can be applied or used.[1,55]

Cutaneous $CD4^+$- Small/Medium-Sized T-Cell Lymphoma

This lymphoproliferative process is listed as a provisional entity in the current WHO classification. Originally considered to be a rare lymphoma form, this lymphoproliferation is nowadays more commonly diagnosed. In most patients, the disease presents clinically with a solitary nodule on the head or neck (**Fig. 9**).

Histologically, a dense nodular infiltrate composed of small to medium-sized lymphocytes with chromatin dense nuclei and a slight nuclear pleomorphism with admixture of eosinophils,

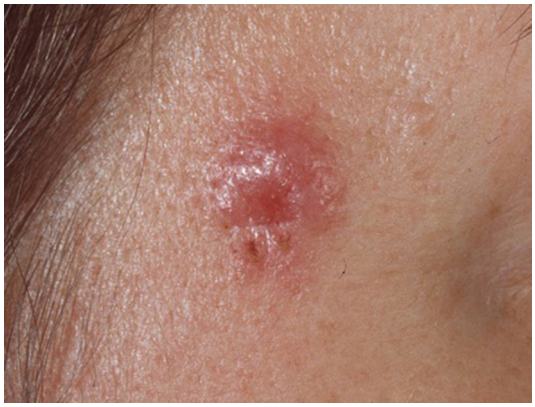

Fig. 9. Cutaneous CD4-positive SMTL: nonulcerated solitary nodule on the right temple.

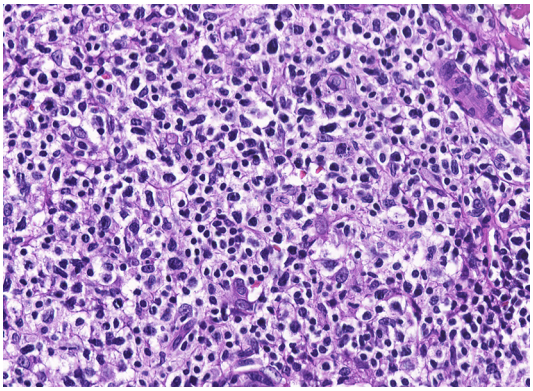

Fig. 11. Cutaneous CD4-positive SMTL: infiltrate of small to medium-sized lymphocytes with slight nuclear pleomorphism. HE, ×200.

plasma cells, and other B cells as well as histiocytes are found (**Fig. 10**). The small to medium-sized lymphocytes express CD4 and a subset of the $CD4^+$ cells also express PD-1 (**Fig. 11**).[56] The expression of PD-1, however, is not restricted to $CD4^+$SMTL, but can be found in various stages of MF, SS, as well as other CTCLs. Therefore, PD-1 cannot be considered a diagnostic marker specific for $CD4^+$SMTL, and additional markers, such as bcl-6, ICOS, CXCL-13, or CD10, need to be expressed by the tumor cells to prove a follicular helper T phenotype. The proliferation rate usually does not extend more than 30%.[34,57] In about 60% of the cases, a clonal T-cell population can be detected.[57] Because of this relatively low detection rate, the value of clonality studies in $CD4^+$ SMTL is limited.

Differential diagnosis includes tumor stage of MF, which can be distinguished by the presence of patches and plaques preceding the development of nodular lesions (**Table 4**). Secondary cutaneous involvement by angioimmunoblastic T-cell lymphoma is based on the results of staging examinations and additional laboratory findings. Infiltrates of cutaneous marginal zone (MZL) B-cell lymphoma have to be considered particularly if there are monotypic plasma cells present. The most challenging differential diagnosis is nodular T-cell pseudolymphoma due to overlapping histologic and phenotypic findings. In 5% of the patients, the development of nodular T-cell pseudolymphoma is linked to drug intake, particularly of antiepileptics.

The prognosis of $CD4^+$ SMTL in its solitary or localized form is excellent with a 5-year survival rate greater than 95%. Patients with multiple lesions, however, and a higher proliferation rate of tumor cells as well as a lower number of infiltrating $CD8^+$ cells carry an impaired prognosis and should be treated more aggressively.[58] In regard to the overlapping features, some authors consider $CD4^+$ SMTL and nodular T-cell pseudolymphoma to represent one disease and therefore refer to the process as primary cutaneous $CD4^+$ small/medium-sized lymphoproliferative disorder to underline its indolent course. Considering the impaired prognosis of $CD4^+$ SMTL presenting with multifocal lesions, this constellation should rather be referred to as PTCL NOS.

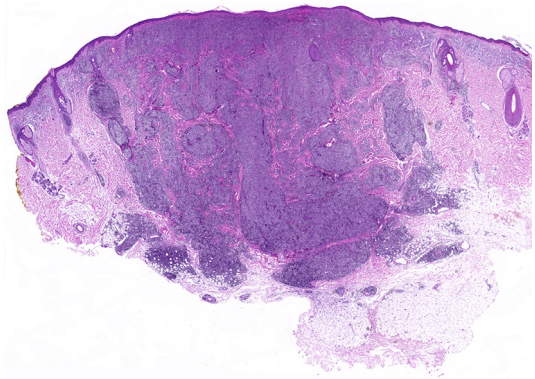

Fig. 10. Cutaneous CD4-positive SMTL: nodular dermal lymphocytic infiltrate without epidermotropism. HE, ×2.5.

Primary Cutaneous $CD8^+$ Aggressive Epidermotropic Cytotoxic T-Cell Lymphoma

This lymphoma is a very rare, but highly aggressive form of CTCL characterized by widespread erosive patches, plaques, papules, and nodules with necrosis and ulceration.[59,60] Men are more commonly affected. Usually the patients are in their fifth to seventh decade at diagnosis. Diagnostic criteria for $CD8^+$ AECTCL include short

Table 4
Nodular infiltrates of small/medium-sized atypical T cells

$CD4^+$ SMTL	Mostly solitary nodules on the head and neck; admixture of B cells. Expression of follicular helper T-cell markers (eg, PD-1, bcl-6, ICOS). Admixture of B cells (in clusters) and plasma cells.
Transformed MF	Patches and plaques Often admixture of large pleomorphic lymphocytes; variable expression of CD30 and PD-1.
Angioimmunoblastic T-cell lymphoma	Often multiple lesions. Admixture of Bcells and plasma cells. Expression of follicular helper T-cell markers. Association with EBV (in 50% of the skin infiltrates).
Nodular T-cell pseudolymphoma	Identical clinical and histologic as well as phenotypic findings as in $CD4^+$ SMTL.

history, widespread lesions, epidermotropism of pleomorphic T cells, a $CD8^+/CD4^-$ phenotype, and an aggressive course as essential diagnostic elements.[61] Histologically, this lymphoma entity is characterized by an epidermotropic infiltrate of small to medium-sized to even large atypical lymphocytes with pleomorphic chromatin dense nuclei (**Fig. 12**). Commonly, apoptotic keratinocytes, spongiosis, intraepidermal vesicles, and blister formation as well as epidermal necrosis can be seen. In addition to the epidermotropic component, a deeper component involving the dermis and subcutis and presenting occasionally with angioinvasive growth can be observed. Phenotyping is crucial for the diagnosis of this lymphoma entity because the tumor cells express a characteristic phenotype ($CD3^+$e, $CD4^+$, $CD8^+$, $CD30^-$, $CD45RA^+$, $CD45RO^-$, $TIA1^+$, and β $F1^+$) (**Fig. 13**). There is no association with EBV.

The differential diagnosis of $CD8^+$ AECTCL is broad and includes primarily $CD8^+$ MF (See **Table 2**). The latter, however, presents with nonulcerated and nonerosive patches and plaques and shows an indolent course in contrast to $CD8^+$ AECTCL. In addition, usually there is no significant number of apoptotic keratinocytes. In addition, LyP type D must be considered, which differs from $CD8^+$ AECTCL by the expression of CD30 (in 90% of the cases) and the lack of expression of CD45RA. Moreover and most importantly, LyP type D shows recurrent papulonodular lesions with spontaneous regression and exhibits an indolent course. As a differential diagnosis among the inflammatory disorders, $CD8^+$, $CD30^+$ PLEVA can be distinguished by the lack of nuclear atypia as is seen in $CD8^+$ AECTCL. Moreover, the clinical presentation differs significantly from $CD8^+$ AECTCL.

Cutaneous γ/δ T-Cell Lymphoma

This rare and aggressive lymphoma is characterized by a clonal proliferation of mature and

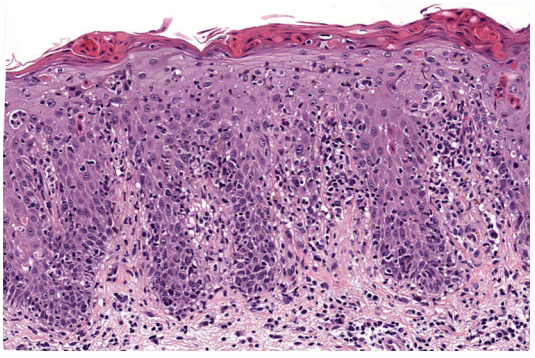

Fig. 12. Cutaneous CD8-positive AETCL: epidermotropic infiltrates of atypical lymphocytes. Note apoptotic keratinocytes. HE, ×200.

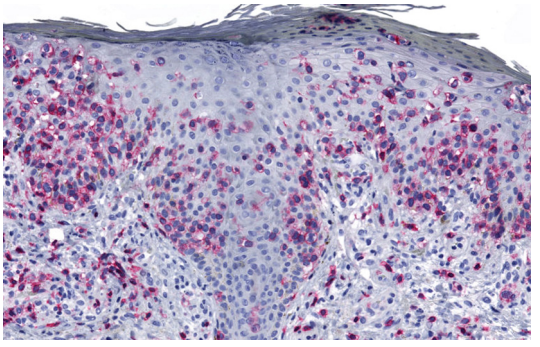

Fig. 13. Cutaneous CD8-positive AETCL: expression of CD8 by the epidermotropic atypical lymphocytes. Immunohistochemistry, ×200

activated γ/δ T cells. Histologically, epidermotropic (pagetoid), dermal diffuse, or nodular or subcutaneous infiltrates or a combination of these patterns can be found.[50,62] In particular, the subcutaneous form of γ/δ T-cell lymphoma is often accompanied by a dermal and an epidermotropic component. In the subcutaneous form, a lobular infiltrate of medium-sized to large cells with chromatin-dense atypical nuclei is present. Angiocentric and angiodestructive infiltrates are common features.[63] The tumor cells exhibit a $CD2^+$, $CD3^+$, $CD56^+$ phenotype being often CD4/CD8-double-negative. In addition, cytotoxic molecules (TIA1, granzyme B, and perforin) are typically expressed. By definition, the tumor cells lack expression of TCR α/β (β F1), but express TCR γ/δ, which can be demonstrated by the expression of TCR γ on formalin-fixed, paraffin-embedded sections or by TCR δ on fresh frozen tissue. Clonality studies reveal a clonal rearrangement of TCR γ/δ. The vast majority of cutaneous γ/δ lymphoma is not associated with EBV, but rare cases of EBV^+ primary cutaneous gamma/delta T-cell lymphoma (PCGD-TCL) have been reported. Cutaneous γ/δ T-cell lymphoma can be accompanied by a hemophagocytic syndrome defined by fever, splenomegaly, cytopenia, hypertriglyceridemia, or hypofibrinogenemia, elevated serum ferritin, $CD25^+$ cells, and the evidence of hemophagocytic histiocytosis in bone marrow, spleen, or lymph nodes.

Differential diagnosis includes the epidermotropic form of PCGD-TCL MF (plaque stage). Because classic MF cases with expression of TCR γ/δ have been documented in the literature, the definite distinction between MF and PCGD-TCL requires, however, careful clinicopathologic correlation and should not only be based on the phenotype of the tumor cells.[64] In the presence of predominantly dermal infiltrates in PCGD-TCL with angiocentric features, other aggressive forms of T-cell lymphomas with angiocentric/angiodestructive infiltrates need to be considered. In this context, one has to be aware that distinction from extranodal NK-/T-cell lymphoma, nasal type may be very challenging, because this lymphoma and PCGD-TCL show overlapping histologic as well phenotypic features. The presence of EBV highlighted by in situ hybridization rather argues for extranodal NK-/T-cell lymphoma, nasal type.

Cutaneous Peripheral T-Cell Lymphoma, Unspecified

PTCL NOS is a very rare form of CTCL that is in most cases associated with an aggressive course. Patients usually present with rapidly growing large solitary ulcerated tumors or disseminated nodular lesions without preceding patches and plaques. Histologically, in most cases diffuse or nodular dense infiltrates of mostly medium to large-sized lymphocytic tumor cells with significant nuclear pleomorphism are found.[65,66] Epidermotropism is found in a subset of cases. An angiocentric component can be present. Eosinophils of variable numbers and plasma cells are admixed. Variable T-cell phenotypes ($CD4^+$ or $CD8^+$ or CD4/CD8-double-negative and -double-positive) with or without expression of cytotoxic proteins are found.[66–68] By definition, most tumor cells do not express CD30.[1] An aberrant expression of CD20, but not additional B-cell markers, can be observed in a subset of cases. Clonal rearrangement can be detected, but is often not required for diagnostic purposes.

The differential diagnosis includes primarily transformed MF, which differs from PCTL NOS by preceding patches and plaques (**Table 5**). Importantly, radiologic staging examinations have to exclude secondary cutaneous involvement by a nodal PTCL NOS. Primary cutaneous or systemic ALCL is distinguished by the expression of CD30 by at least 75% of tumor cells. The differentiation from extranodal NK-/T-cell lymphoma and γ/δ T-cell lymphoma is primarily based on the phenotype (EBV-positivity) in extranodal NK-/T-cell lymphoma and expression of TCR γ/δ in PCGD-TCL. Adult T-cell leukemia/lymphoma shows an association with HTLV1, which is not present in PCTL NOS.

Extranodal Natural Killer-/T-Cell Lymphoma, Nasal Type

This rare, but aggressive form of lymphoma is characterized phenotypically by a phenotype resembling NK/T cells and NK cells. Hydroa vacciniformia-like lymphoma represents a variant of EBV^+ NK-/T-cell lymphoma occurring mostly in Central and South America in young adults and children.[69,70] Facial or periorbital edema is typically found. Skin lesions further include blister formation and ulcerations, particularly on sun-exposed areas.

The histology shows predominantly angiocentric and angiodestructive infiltrates of tumor cells of variable size with nuclear pleomorphism and mitotic activity. Usually numerous eosinophils, plasma cells, and histiocytes can be observed. Phenotypically, the tumor cells lack expression of surface CD3, but express CD3ε, CD56, and cytotoxic markers.[71,72] Most importantly, EBV can be demonstrated by in situ hybridization or immunohistochemistry.

Table 5
Large T-cell lymphoid infiltrates: differential diagnoses

Cutaneous anaplastic large cell lymphoma	Solitary or grouped ulcerated nodule or nodules. Expression of CD30 by more than 75% of the tumor cells.
LyP (type C)	Recurrent papules and nodules. Expression of CD30 by the large atypical lymphocytes.
MF, transformation	Patches, plaques (and tumors). Presence of more than 25% of large pleomorphic cells with variable expression of CD30. Variable loss of T-cell markers. Admixture of B cells possible.
Primary cutaneous peripheral T-cell lymphoma, unspecified	Solitary or multiple nodules/tumors. Variable phenotype (cytotoxic vs noncytotoxic, CD4 vs CD8 or double-negative); expression of CD30 by <30% of the cells.
Extranodal NK-/T-cell lymphoma, nasal type	Ulcerated tumors. Angiocentric and angiodestructive growth. Expression of $CD3\varepsilon^+$, $CD56^+$, $EBER^+$.
Cutaneous γ/δ-T-cell lymphoma	Erosive or ulcerated plaques and tumors. Expression of $CD3^+$ $CD8^+$ $TCR\gamma^+$ $EBER^-$.

CUTANEOUS B-CELL LYMPHOMAS

Cutaneous B-cell lymphomas are the second most common group of CLs, accounting for about 25% to 35% of all CLs.[73]

Primary Cutaneous Marginal Zone Lymphoma

In the WHO classification, primary cutaneous marginal zone lymphoma (PCMZL) belongs to the group of extranodal MZL of mucosa-associated lymphoid tissue (MALT-lymphoma).[74,75] Recent data indicate that PCMZL differs from other MALT-lymphoma with regard to the expression of class-switched immunoglobulins, chemokine receptors, translocations, and associated infections.[76,77] In the WHO-EORTC (European Organization For Research and Treatment of Cancer) classification and WHO classification, cutaneous immunocytoma, and primary cutaneous plasmocytoma are considered to represent variants of PCMZL.[1,78] These variants are characterized by a dense dermal infiltrate, which is almost entirely composed of plasma cells with monotypic expression of Ig light chains.[1,78] A systemic manifestation has to be excluded by staging procedures. An overview of the diagnostic characteristics is given in **Table 6**.

Histology

PCMZL is characterized by a nodular dermal lymphocytic infiltrate, separated from the uninvolved epidermis by a grenz zone and sometimes extending into the subcutaneous fat (**Fig. 14**). The infiltrate consists of small lymphocytes, lymphoplasmacytoid cells, and plasma cells, which are commonly located in the edge of the infiltrates and next to the epidermis (**Fig. 15**). Reactive germinal centers can be seen. The infiltrate is typically accompanied by abundant admixed T lymphocytes.

Morphologic variants of PCMZL are reported with (i) marked plasmacytoid differentiation,[79] (ii) a high number of admixed T lymphocytes,[79] (iii) a predominance of monocytoid B cells instead of lymphoplasmocytoid cells. A blastic transformation is a rare event in PCMZL and has been linked to an aggressive clinical course. Because of a reported CD5 and CD23 expression,[80] these lesions have to be differentiated from B-cell chronic lymphocytic leukemia (B-CLL) with large cell transformation (so-called Richter transformation).[81]

Two subtypes of PCMZL have been described based on different expression profiles of immunoglobulins[76,77]: (i) the more common class-switch form, which predominantly consists of a nodular and perivascular infiltrate with numerous admixed T cells. The plasma cells express IgG, IgA, or IgE. An IgD expression is found in reactive lymph follicles. The B cells lack CXCR3; (ii) the rare non-class-switch form, which presents with larger nodular dermal infiltrates predominantly composed of B cells. The number of admixed T cells is only moderate. The plasma cells express IgM. The CXCR3 expression is strong in T and

Table 6
Cutaneous B-cell lymphomas

	Cutaneous Marginal Zone Lymphoma	Cutaneous Follicle Center Lymphoma	Diffuse Large B-Cell Lymphoma, Leg Type	Diffuse Large B-Cell Lymphoma, Other
Pattern	Nodular, geographic	Nodular, diffuse	Diffuse	Diffuse
Infiltrate composition	Small lymphocytes, lymphoplasmocytoid cells, plasma cells	Predominantly centrocytes	Predominantly centroblasts and immunoblasts	Predominantly centroblasts and immunoblasts
Follicular structures	Reactive GC (bcl6+, bcl2−)	In follicular growth pattern: neoplastic follicles (bcl6+, bcl2−/+)	No germinal centers	No germinal centers
Phenoytpe	CD20/CD79a/PAX5+ bcl2+, bcl6− κ, λ	CD20/CD79a/PAX5+ bcl2−, bcl6+, MUM-1−, IgM−, irregular networks of FDC (CD21+/CD35+)	CD20/CD79a/PAX5+ bcl2++, bcl6−/+, MUM-1+, IgM+, lack of FDC networks (CD21/CD35)	CD20/CD79a/PAX5+ bcl2−, bcl6+, MUM-1+/−, IgM−, FOX-P1 +/− lack of FDC networks (CD21/CD35)
Genetics	t(14;18)(q32;q21)IGH/BCL2 and t(14;18) (q32,q21) IGH/MALT translocation is an indicator for transformation toward higher-grade B-cell lymphoma.	t(14;18) translocation was found in up to 50%. This translocation was not linked to differences in clinical presentation and prognosis. Deletion of chromosome 14q32.33 has been reported.	Translocations involving MYC, BCL6, IGH genes. High levels of DNA amplifications of 18q21.31-q21.33, including BCL2 and MALT genes. Loss of 9p21 is a negative prognostic marker. Chromosomal imbalances with gains in 18q and 7p and loss of 6q.	

Abbreviation: GC, germinal centers.

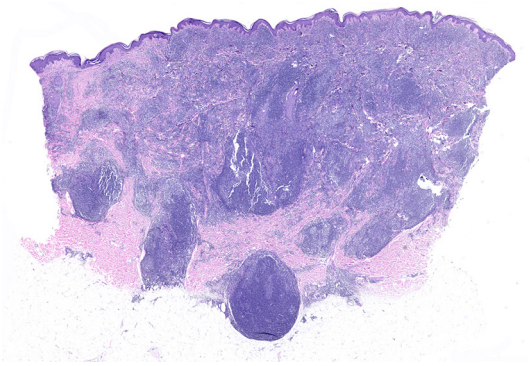

Fig. 14. Cutaneous MZL: dermal and superficial subcutaneous nodular and confluent lympohcytic infiltrate. Note the grenz zone beneath the epidermis. HE, ×2.5.

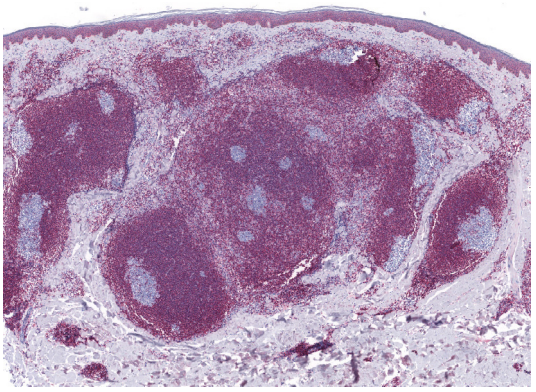

Fig. 16. Cutaneous MZL: expression of bcl-2 by tumor cells. Note the spared reactive germinal centers. HE, ×5.

mild in B cells. In the non-class-switched form, extracutaneous involvement is more often observed.

In contrast to noncutaneous MZL, IgG4 expression is found in approximately 40% of PCMZL and may represent a marker for PCMZL.[82]

Immunophenotype and clonality

The tumor cells express CD20, CD79a, and bcl-2 and are negative for bcl-6, CD5, CD10, and CD43 (**Fig. 16**).[1,83] Plasma cells could be highlighted by CD138. To detect monotypic plasma cells, immunohistochemistry or in situ hybridization must be performed. Most experts consider monoclonal a ratio of 5:1 or 10:1. Monotypic plasma cells can be found in 85% of the cases[84]: in two-thirds of cases, kappa is predominant,[84] and a heavy chain rearrangement is detected in about 60% to 70% of the cases.[84]

Genetics

t(14;18) (q32;q21) IGH/BCL2 and t(14;18) (q32;q21) IGH/MALT-1 were seen in cases of PCMZL with transformation toward higher-grade B-cell lymphoma.[85]

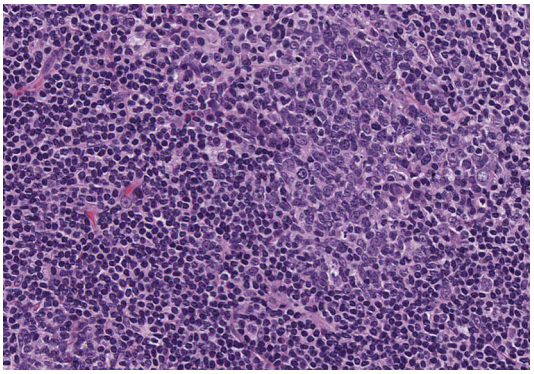

Fig. 15. Cutaneous MZL: proliferation of small lymphocytes in the interfollicular component and reactive germinal centers. HE, ×200.

Differential diagnosis

Distinction of PCMZL from cutaneous B-cell pseudolymphoma (B-PSL), which shows similar features as PCMZL with small B cells, plasma cells, and reactive germinal centers, is based also on clinical presentation (mostly solitary lesion in B-PSL, characteristic predilection sites of ears, scrotum, and nipples in Borrelia-associated B-PSL [Synonym Borrelia-associated lymphocytoma cutis] and a polytypic expression of Ig light chains in B-PSL). In primary cutaneous follicle center cell lymphoma (PCFCL), the tumor cells show a centrocyte-like differentiation. Plasma cells are usually sparse or absent in PCFCL. Cutaneous involvement by B-cell chronic lymphocytic leukemia (B-CLL) may sometimes simulate PCMZL and could be differentiated by their immunohistochemical profiles. In contrast to PCMZL, the tumor cells in B-CLL express CD5, CD23, and CD43.[83,86] Another diagnostic pitfall is a secondary cutaneous infiltrate of extracutaneous MALT lymphoma, which must be excluded by staging procedures. It remains a matter of debate whether PCMZL represents a de novo neoplastic process or whether B-PSL and PCMZL represent different evolutionary steps of the same disease. Therefore, a clear differentiation between both entities could be difficult or impossible in individual cases. Monotypic plasma cells or a monoclonal IgH rearrangement (same clone in repeated assays) argues for a PCMZL. In certain areas of Europe, PCMZL is rarely associated with *Borrelia burgdorferi* infection, but this link has not been found in PCMZL from Asia and the United States.[87–89]

In plasma cell predominate variants (primary cutaneous plasmocytoma, immunocytoma), other differential diagnoses have to be considered.

Secondary cutaneous plasmocytoma could be excluded by staging procedures. Rare, but important differential diagnoses are vegetating herpes virus infections in HIV patients,[90] lymphoplasmacytoid plaque,[91,92] and cutaneous plasmocytosis.[93] These entities can show a plasma cell–rich infiltrate, but the plasma cells are polyclonal in contrast to most cases of PCMZL.

Primary Cutaneous Follicle Center Lymphoma

PCFCL is listed as a separate entity in the WHO classification.[74] It is characterized by a tumor of neoplastic follicle centers and is predominantly composed of centrocyte-like cells. It occurs typically on the scalp, large tumors of PCFCL on the back that had been originally referred to as reticulohistiocytoma dorsi (Crosti lymphoma). Miliary and agminated types of PCFCL can be challenging, histologically and clinically.[94] The diagnostic criteria are given in **Table 6**.

Histology

Three growth patterns can be discerned, but in all of them, a proliferation of tumor cells with centrocyte-like differentiation predominates (**Fig. 17**):

i. The follicular growth pattern is characterized by predominantly large neoplastic follicles, which are composed of centrocyte-like cells. Tingible body macrophages are only rarely found (less than 10%).
ii. The diffuse growth pattern is defined by diffuse aggregates of medium and large centrocytes with admixed small lymphocytes. Follicular structures cannot be detected.
iii. In the mixed growth pattern, areas with diffuse arrangement of centrocyte-like cells, next to areas with follicular structures, can be observed.

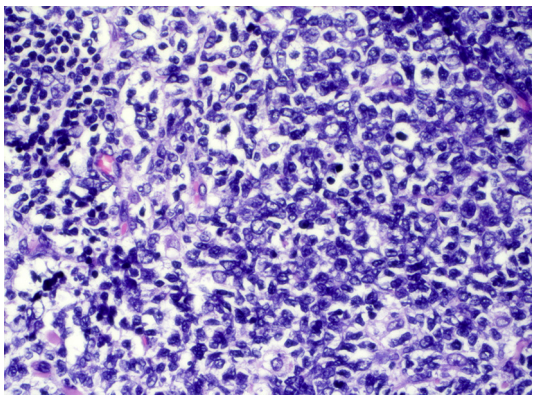

Fig. 17. Cutaneous follicle center lymphoma: proliferation of tumor cells with centrocyte-like differentiation. HE, ×200.

As a morphologic variant of PCFCL, a spindle cell differentiation has been described.[95]

Cases with coexpression of CD30 or with blastic transformation can cause diagnostic difficulties.[96,97]

Immunophenotype and clonality

The tumor cells in PCFCL express CD20, CD79a, PAX-5, and bcl-6. They are predominantly negative for bcl-2 (90%), in contrast to nodal follicular lymphoma.[98] The presence of bcl-2 expression or t(14; 18) translocation in PCFCL is not linked to differences in clinical presentation or prognosis.[1] Proliferating cells (Ki-67+ or MIB-1+) are scattered throughout the entire infiltrate. CD21 highlights large irregular networks of follicular dendritic cells (FDC). FOX-P1 expression is an indicator for a worse prognosis.[99] A heavy chain rearrangement could be detected in about 90% of the cases (BIOMED-2 protocol).[100]

Genetics

In nodal follicular lymphoma, t(14;18) translocation is presented in approximately 90% of cases. In PCFCL t(14;18), translocation was found in up to 50%, but was not linked to differences in clinical presentation and prognosis.[1,98] Deletion of chromosome 14q32.33 has been reported.

Differential diagnosis

Some B-PSLs show features accounting for a significant overlap with PCFCL.[101,102] In those cases, coalescing lymphoid follicles with nonpolarized germinal centers lacking mantle zones and smudged infiltrate of lymphoid cells spreading into collagen (often as single cell files), smooth muscle, vessel walls, and peripheral nerve sheets may result in diagnostic challenge and mimic PCFCL. In cases with germinal centers, in B-PSL the proliferative activity (Ki-67$^+$ or MIB-1$^+$) and bcl-6 expression are more restricted to the germinal centers. Tingible body macrophages are more often found in B-PSL.[103] The networks of CD21-positive FDCs are more sharply restricted to the germinal centers.

Comparing CBCL, recent publications have demonstrated that PD-1 expression is significantly higher in PCMZL and PCFCL in contrast to primary cutaneous diffuse large B-cell lymphoma-leg type (PCDLBCL-LT) and showed PD-1-positive cells forming so-called pseudorosettes or clusters. The tumor cells themselves were negative for PD-1.[34,104] Moreover, clusters of CD123-positive plasmocytoid dendritic cells have been described, which are found in only a minority of PCFCL and are absent in PCDLBCL-LT.[105]

Distinction of PC-FCL from secondary cutaneous infiltrates of nodal follicular lymphoma, which often show expression of bcl-2, requires staging. Secondary cutaneous involvement of mantle cell lymphoma has to be considered in the differential diagnosis. The diffuse infiltrates are composed of blasts and centrocyte-like tumor cells. The tumor cells are positive for CD5 and cyclin D1, but negative for CD23.[106]

Primary Cutaneous Diffuse Large B-Cell Lymphoma-Leg Type

PCDLBCL is characterized by dense nodular or diffuse infiltrates predominated by centroblast-like and immunoblast-like tumor cells with noncleaved, round nuclei.[1] The PCDLBCL-LT represents the most common type of diffuse large B-cell lympoma (DLBCL) and is listed as a distinct subtype of DLBCL in the current WHO classification.[3] The diagnostic criteria are outlined in **Table 6**.

Histology

There is a diffuse dermal infiltrate of centroblast-like and immunoblast-like cells with mitotic activity and only a few admixed reactive lymphocytes (**Fig. 18**). Epidermal involvement is uncommon and rarely described. Usually a subepidermal grenz zone can be found. An infiltration in the subcutis can be observed. An uncommon histologic presentation includes a spindle cell and an anaplastic variant.[107] Moreover, an angiocentric infiltrate[108] and expression of CD30 have been described.[109,110]

Immunophenotype and clonality

The tumor cells are positive for CD20, CD79a, and PAX-5 and show a strong expression for bcl-2 and multiple myeloma oncogene-1 (MUM-1). In most cases, they are negative for bcl-6 and CD10 or show only a weak expression.[111] IgM expression was identified as an additional adjunctive diagnostic marker, which is found in all cases of DLBCL-LT but only rarely in PCFCL (9%).[112] Networks of CD21-positive FDC are not found. FOXP1 expression was linked to a worse prognosis.[99]

A diagnostic pitfall may result from CD30 expression in large B-cell lymphoma mimicking ALCL, but expression of CD20 and absence of T-cell markers led to the diagnosis.[109,110] PD-1 expression is significantly lower in PCDLBCL-LT than in PCMZL and PCFCL.[34,104] The tumor cells are predominantly negative for PD-1, but in some cases an expression of PD-1 in the tumor cells can be observed.[34,104] There may be detection of heavy chain rearrangement by PCR.

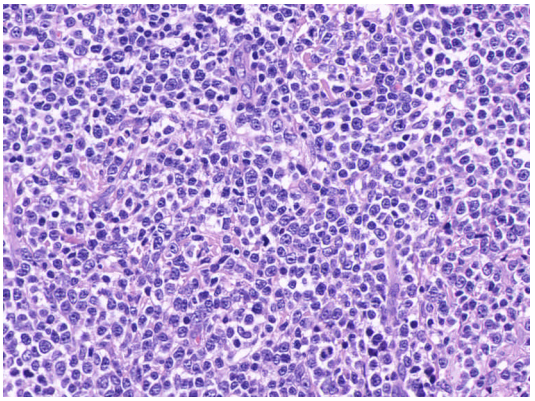

Fig. 18. Cutaneous diffuse large B-cell lymphoma, leg type: cohesive sheets of blasts resembling centroblasts and immunoblasts. HE, ×200.

Genetics

Genetic analysis has revealed chromosomal loss of 9p21, which encodes p16 as a negative prognostic marker in PCDLCBL-LT.[113] Loss of p16 assessed by immunohistochemistry, however, does not correlate with these findings, indicating the necessity for genetic analysis by reverse transcription–PCR or FISH analysis. Recurrent deletions in 9p21 (p14 [ARF]/p16 [INK4a/CDKN2A]) have been found to be a constant finding in PCDLBCL-LT, whereas PCFCL does not exhibit this change.[114] Chromosomal imbalances have been identified in up to 85% of PCDLCBL-LT, with gains in 18q and 7p and loss of 6q as the most common findings.[115,116] A high prevalence of MYD88L265P mutation shows an association with a shorter survival.[117]

Differential diagnosis

Secondary cutaneous involvement has to be excluded by staging procedures. The most important differential diagnosis of PCDLBCL-LT is PCFCL with a diffuse growth pattern. The tumor cells of PCFCL are predominantly negative for bcl-2 and positive for bcl-6 and CD10. Networks of FDCs cannot be found in the vast majority of PCDLBCL-LT. IgM expression has been identified as an additional adjunctive diagnostic marker, which is found in all cases of PCDLBCL-LT but only rarely in PCFCL (9%).[112] In sharp contrast to PCDLBCL-LT, the tumor cells of PCDLBCL-other express bcl-6 in all cases and are negative for bcl-2.

Primary Cutaneous Diffuse Large B-Cell Lymphoma-Other

The term PCDLBCL-other refers to cases of large B-cell lymphomas not belonging to PCDLBCL-

LT.[1] PCDLBCL-other is a very rare and still poorly characterized form of DLBCL that shares cytologic features with PCDLBCL-LT. Histologically, PCDLBCL-other presents with a diffuse infiltrate of centroblast-like and immunoblast-like cells with mitotic activity. Occasionally, numerous small lymphocytes in addition to the large centroblast-like and immunoblast-like tumor cells may be present. Anaplastic, plasmablastic, and T-cell/histiocyte-rich variants have been described.[1] The tumor cells express bcl-6 in all cases and are negative for bcl-2. Expression of MUM-1 is found in 67%. FOX-P1 is positive in 50% of the cases.[99] In sharp contrast to PCDLBCL-LT, the tumor cells of PCDLBCL-other express bcl-6 in all cases and are negative for bcl-2.[99] Secondary cutaneous involvement by nodal DLBCL has to be excluded by staging procedures.

Intravascular Large B-Cell Lymphoma

Intravascular large B-cell lymphoma is a rare form of extranodal large B-cell lymphoma. As the designation implies, intravascular large B-cell lymphoma is characterized by the intravascular growth of large B cells, especially in small vessels, particularly capillaries and venules (**Fig. 19**).[118] A defect in homing receptors on tumor cells (CD29 = β1 Integrin; CD54 = ICAM1) is considered to be responsible for the unique intravascular growth pattern.[119] Any organ can be involved, although lymph nodes are usually spared. A systemic form and a cutaneous form are distinguished. Histology of skin lesions shows small dermal and subcutaneous vessels filled with large B cells with pleomorphic, moderately chromatin dense nuclei and abundant cytoplasm. Occasionally, tumor cells colonize in hemangiomas.[120,121]

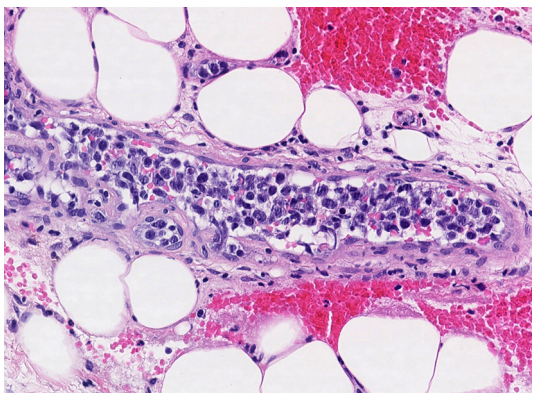

Fig. 19. Intravascular large B-cell lymphoma: accumulation of blasts within small vessels in the subcutis. HE, ×200.

The tumor cells express CD20 and bcl-2 and may be positive for CD5 or CD10.

Differential diagnosis includes other forms of intravascular lymphomas and reactive intralymphatic accumulations of lymphocytes. A rare T-cell and NK cell variant of intravascular lymphomas has been described and is associated in some cases with EBV.[122] Iacobelli and colleagues[123] reported a case of intravascular ALCL restricted to the skin. The T-cell and NK-cell variant is not included as a distinct entity or subtype in the current WHO classification. Differential diagnosis includes intralymphatic histiocytosis as it can be seen after orthopedic metal implantation.[124] Benign intravascular CD30+ T-cell proliferation occurring after trauma or as a consequence of inflammatory skin diseases has to be differentiated from the rare T-cell variant of intravascular lymphoma.[125,126] The distinction could be easily made by immunohistochemistry.

Epstein-Barr Virus–Associated B-Cell Lymphoproliferations

EBV is a γ-herpes virus, which is associated with a range of lymphoproliferative disorders. Among the increasing spectrum of EBV-associated B-cell lymphoproliferations, EBV-positive DLBCL of the elderly, plasmablastic lymphoma, EBV-positive mucocutaneous ulcer, lymphomatoid granulomatosis posttransplant, and methotrexate (MTX)-associated B-cell lymphoproliferative diseases are of particular dermatopathologic interest.[127] An overview of the diagnostic characteristics of EBV-associated lymphoproliferations in the skin is given in **Table 7**.

EBV-positive DLBCL of the elderly is an EBV-positive B-cell lymphoma that occurs in patients older than 50 years of age (with a median age of 71 years) and without any known immunodeficiency or previous lymphoma (see **Table 7**).[128] Nevertheless, the immunologic deterioration or senescence in immunity as part of the aging process is assumed to play a pathogenetic role in the development of this lymphoma, which involves most commonly extranodal sites (70%), especially skin, lung, tonsil, and stomach. The primary cutaneous form is very rare.

Plasmablastic lymphoma is a rare variant of DLBCL that almost exclusively develops in the setting of HIV infection or other immune deficiencies, including posttransplant.[129,130] Risk factors for the development of the lymphoma in the setting of organ transplantation include younger age, higher rejection frequency, and high-dose cyclosporine therapy.

Table 7
Overview of the diagnostic characteristics of Epstein-Barr virus–associated lymphoproliferations in the skin

	EBV-Positive DLBCL of the Elderly	EBV-Positive Mucocutaneous Ulcer	MTX-Associated B-Cell Lymphoproliferative Disease	Posttransplant Lymphoproliferative Disorder	Plasmablastic Lymphoma	Lymphomatoid Granulomatosis
Histology	Diffuse infiltrate of immunoblast-like or plasmablast-like cells. Intermingled tingible body macrophages. Geographic necrosis.	Ulceration. Polymorphous infiltrate, mixture of lymphocytes and immunoblasts. Often Hodgkin-/Reed-Sternberg-like cell morphology. Dispersed apoptotic cells. Abundant small T cells in the background. Scattered plasma cells, histiocytes, and eosinophils. "Cartwheel" nuclear appearance of plasma cells. Angio-invasion with associated thrombosis may be found.	Diffuse infiltrate of centroblasts and immunoblasts. Some polymorphous tumor cells with a Reed-Sternberg-like appearance. Admixed T cells. The EBV-cases were more monomorphous with either centrocytes or immunoblasts.	Dense diffuse or nodular monomorphous infiltrates of centroblastic, immunoblastic, or plasmablastic cells. Often numerous mitotic figures.	Diffuse or multinodular proliferation. Immunoblast-like cells or markedly atypical cells with plasmablastic differentiation. Eccentric nucleus with a "clock-faced" chromatin, a discrete perinuclear hof and abundant cytoplasm. Multinucleated forms can be observed. Numerous/atypical mitotic figures.	Skin involvement found in 40%–50% of the cases. Patchy infiltration of the dermis and subcutis, only little or no epidermal involvement. Angiocentric lymphohistiocytic infiltrate with lymphocytic angiitis and admixed atypical B cells. Multifocal areas of necrosis.

Phenotype	CD20+,CD79a+, PAX-5+, MUM-1/IRF4+, CD10−, bcl-6−, CD30+/−, light chain restriction +/−, Ki-67/MIB-1+++	CD30++, CD20(+/−), CD45+ (56%), CD15+ (43%), PAX-5+, Oct-2+, MUM-1+, CD10−, bcl6+/− (focal)	CD20(+), PAX5+, CD79a(+), MUM-1+ (80%), FOXP1+ (70%), bcl-2+ (80%), bcl-6 (70%), CD30+ (60%). Reduced expression of B-cell markers in EBV+ cases.	CD20+ or CD79a, MUM-1+, Ki-67/ MIB-1+++	CD20−, PAX-5-, CD38+ CD138+, VS38c+, CD10+/−, CD79a+/−, CD30+/−, CD56+/−	Predominating CD3/ CD4+ T-cell infiltrate with scattered atypical CD20+ B cells.
Viruses	In situ hybridization for EBER. Some cases also show expression of latent membrane protein 1 and EBNA-2.	The CD30+ B cells were positive for EBER.	EBER is positive in 50% of the cases.	EBV detection (in situ hybridization or PCR) in 90% of the cases.	EBV has been demostrated in most cases. EBER transcripts often found in virtually all tumor cells. HHV-8 has also been implicated in this lymphoma type.	Association with EBV was found in most cases with EBER transcripts present in B cells.

Abbreviations: EBNA-2, epstein barr virus nuclear antigen-2; HHV-8, human herpesvirus 8.

Lymphomatoid granulomatosis is a rare B-cell proliferation with primarily extranodal involvement, affecting the lungs, skin, central nervous system, and kidneys. The skin is secondarily involved in 20% to 50% of patients with lymphomatoid granulomatosis.[131] Histologically, angiocentric infiltrates with large atypical B cells are found in a background of a dense infiltrate of reactive T cells, histiocytes, and plasma cells.[132,133] Association with EBV is found in most of the cases with EBER transcripts present in B cells.

EBV-positive mucocutaneous ulcer is a recently described B-cell lymphoproliferative disease that manifests with isolated sharply demarcated ulceration most commonly in the oropharynx, skin, and gastrointestinal tract (see **Table 7**).[134] One-third of the affected patients have a drug-related immunosuppression, but age-related immune suppression is also a feature.[134,135] Polymorphous infiltrates of atypical large B-cell blasts, often with Hodgkin or Reed-Sternberg cell-like morphology in the background of abundant small T cells and eosinophils, are found. The large cells express CD20 and CD30 and are positive for EBER.[134]

Posttransplant B-cell lymphoproliferative disorders represent a spectrum of lymphoid tissue disease, ranging from early lesions, such as plasmacytic hyperplasia, to monomorphic neoplasm.[136] They usually manifest years after transplantation, are frequently EBV linked, and are associated with a favorable clinical outcome.[136]

Methotrexate-associated B-cell lymphoproliferative disease presents with ulcerating or generalized skin lesions. Histologically, it shares features with PCDLBCL-LT.[137] In cases with a reduced staining for CD79a and marked tumor cell polymorphism, this diagnosis should be taken into account.

SUMMARY

Considering the overlap in clinical presentation and histologic as well as phenotypic features of CLs, the final diagnosis in cutaneous lymphoproliferative disorders must be based on a multiparameter approach integrating clinicopathologic correlation and detailed phenotypic studies. Molecular studies are indicated in selected cases, but will most probably become more important in the near future to identify prognostic factors and therapeutic targets.

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