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REVIEW

Classification of cutaneous lymphomas – an update

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Classification of cutaneous lymphomas – an update

This review focuses on the evolution and conceptual aspects of classifications for cutaneous lymphomas. The World Health Organization/European Organization for Research and Treatment of Cancer (WHO/EORTC) classification and the WHO classification (4th edn, 2008) represent the first widely accepted classifications for lymphomas, in which the complete spectrum of primary cutaneous lymphomas is included. These classifications for primary cutaneous lymphomas define disease entities with distinct clinical, histological, immunophenotypic and genetic features. Final diagnosis is based on a synoptic integration of these features and implies clinicopathological correlation as a pivotal element of the diagnostic approach for primary cutaneous lymphomas. The entities, their definitions and diagnostic criteria of cutaneous lymphomas listed in the WHO/EORTC and WHO classifications are presented. Recent changes in the terminology and staging, practical implications and future perspectives are discussed.

Keywords: classification, cutaneous lymphoma, diagnosis, WHO, WHO/EORTC

Abbreviations: ALCL, anaplastic large cell lymphoma; CBCL, cutaneous B-cell lymphoma; CD4+ SMPTL, primary cutaneous CD4+ small/medium T-cell lymphoma; CD8+ AETCL, aggressive (epidermotropic) CD8+ T-cell lymphoma; CL, cutaneous lymphoma; CTCL, cutaneous T-cell lymphoma; EORTC, European Organization for Research and Treatment of Cancer; GSS, granulomatous slack skin; LPD, lymphoproliferative disorder; LyP, lymphomatoid papulosis; MALT, mucosa-associated lymphoid tissue; MF, mycosis fungoides; NHL, non-Hodgkin lymphoma; NK, natural killer; PCALCL, primary cutaneous anaplastic large cell lymphoma; PCDLBCL, primary cutaneous diffuse large B-cell lymphoma; PCFCL, primary cutaneous follicle centre lymphoma; PCMZL, primary cutaneous marginal zone B-cell lymphoma; PDC, plasmacytoid dendritic cell; PSL, pseudolymphoma; PTL, NOS, peripheral T-cell lymphoma, unspecified; REAL, Revised European–American Classification of Lymphoid Neoplasms; SPTCL, subcutaneous panniculitis-like T-cell lymphoma; SS, Sézary syndrome; TCR, T-cell receptor; TIA-1, T-cell intracytoplasmic antigen-1; TRAF-1, tumour necrosis factor receptor-associated factor-1; WHO, World Health Organization

Introduction

Primary cutaneous lymphomas (CL) are the second most common form of extranodal non-Hodgkin lymphoma (NHL) and represent a heterogeneous group of neoplasms with a wide spectrum of clinical, histological and immunophenotypical features.[1,2] Primary CL arises in the skin, is restricted to the skin at the time of diagnosis and staging, and often remains confined to the skin for longer periods of time. Secondary CL represents infiltrates of a disseminated nodal or extranodal lymphoma into the skin.

Alibert published the first description of mycosis fungoides (MF) in 1806. Bazin described the patch, plaque and tumour stage as evolutionary stages of this disease in 1870.[3,4] In 1938 Sézary and Bouvrain described Sézary syndrome (SS).[5] Despite these seminal

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articles, CLs were not recognized as a separate group of lymphomas until the seventies of the 20th century. Early classifications of lymphomas did not distinguish between nodal and extranodal, including cutaneous forms of NHL. Most forms of CL were regarded as cutaneous manifestations of a systemic lymphoma and treated according to this concept. Furthermore, those classifications were based exclusively on cytomorphology and immunophenotype of the tumour cells. Primary CLs, however, differ in its biological behaviour and prognosis from histologically or phenotypically similar nodal and other extranodal lymphomas. This has an important impact on the classification and treatment of CL. Based on this pivotal premise, the European Organization for Research and Treatment of Cancer (EORTC) and the World Health Organization (WHO)/EORTC classifications were created to emphasize the unique features of primary CL.[6–8] The nosological entities defined by the WHO/EORTC classification have been adopted by the recent WHO classification (4th edn, 2008), which integrates all forms of primary CL into a larger classification of nodal and extranodal lymphomas.[9]

This article reviews the evolution and basic principles of the WHO/EORTC and WHO classifications. Entities of primary CL and their variants as well as the characteristic clinicopathological and prognostic features are presented. The practical implications for the diagnostic work-up and perspectives for future classifications are discussed.

Basic principles and evolution of lymphoma classifications

The evolution of classifications for nodal and extranodal lymphomas reflects the change in concepts of diagnostic criteria and the stratification of lymphomas as well as our understanding of the pathogenesis of these neoplasms. Classifications ideally should contain diseases that are clearly defined, clinically distinctive and non-overlapping, and comprise all known entities.[10] The basic principle of stratifying lymphoid neoplasms according to the lineage and stage of differentiation of the tumour cell of a lymphoid neoplasm was introduced by the Kiel classification.[11] This form of stratification was pursued by all following classifications. The Revised European–American Classification of Lymphoid Neoplasms (REAL) classification was developed by the International Lymphoma Study Group and published in 1994.[12] It was the first worldwide consensus classification for haematological malignancies. In addition, it represented a paradigm shift by defining distinct ('real') disease entities instead of classifying lymphomas according to their growth pattern, the cell type or the morphology of tumour cells.[13] In the REAL classification, the nosological entities were defined by their histological, immunophenotypic and genetic features. Therefore, the REAL classification was the first lymphoma classification based on a multiparameter approach.[12] Furthermore, the REAL classification distinguished for the first time between nodal and extranodal forms of lymphoma and their differences. As a consequence, the site of involvement had clearly to be stated in the diagnostic reports. This aspect prompted oncologists and pathologists to understand that lymphomas of identical morphology, but different site of primary presentation, may differ as regards their biological behaviour and prognosis.

To emphasize the unique features of primary CL, the EORTC developed a new classification specifically designed for primary CL. The *EORTC classification for cutaneous lymphomas* was published in 1997 and represented the first consensus classification for primary CL.[6] The basic principle was identical to the REAL classification, i.e. to define nosological entities with distinct clinicopathological features. The clinical manifestation was emphasized as an essential element in the diagnostic approach to primary CL. As a consequence, the diagnosis in primary CL can therefore only be achieved by an integration of clinical, histological, immunophenotypic and genetic findings in the context of clinicopathological correlation.

Many classification schemes separated lymphomas into several broader categories of biological behaviour or prognosis. This fact reflects the basic requirement of clinicians to use classifications as tools to pre-estimate the course and prognosis of a lymphoma. The therapeutic strategy in lymphomas and other malignancies is essentially based upon this prognostic categorization. The Working Formulation and Kiel classification stratified lymphomas into low-grade, intermediate and high-grade malignant lymphomas based primarily on tumour cell size.[11,14] The categories in more recent classifications were based on prognostic data from large CL registries such as the Dutch Cutaneous Lymphoma Working Group and the lymphoma registry in Graz, Austria.[6,15] Based on these data, the EORTC classification for CL distinguished between primary CLs with an indolent, intermediate and aggressive clinical behaviour, which allowed a more precise categorization of CL patients than by the WHO classification (3rd edn, 2001).[15]

The EORTC classification was undoubtedly a major breakthrough in the classification of CL and boosted understanding of the unique features of CL. The clinical utility of the EORTC classification and its reproducibility were demonstrated in large studies with data on

>1300 patients with primary CL.[16] Nevertheless, the restriction to primary CL and significant differences from the REAL classification as regards the definitions and diagnostic criteria for certain entities were major reasons that the EORTC classification finally did not gain wide acceptance among pathologists and oncologists.

The REAL classification was updated and adopted by the WHO classification for lymphoid neoplasms, 3rd edn, published in 2001.[17,18] In the WHO classification, most cutaneous T-cell lymphomas (CTCL) were included.[19] The definitions and the diagnostic criteria for cutaneous B-cell lymphoma (CBCL) in the EORTC classification, however, differed significantly from those in the REAL classification and the WHO classification (3rd edn, 2001). In the group of low-malignant CBCL, the EORTC classification distinguished between primary cutaneous follicle centre cell lymphoma and primary cutaneous immunocytoma.[6] In the WHO classification, immunocytoma referred to a distinct systemic lymphoma often associated with Waldenström macroglobulinaemia and extranodal immunocytoma in the group of extranodal marginal zone B-cell lymphomas [mucosa-associated lymphoid tissue (MALT)-type lymphoma].[17] A major debate arose from the fact that primary cutaneous follicle centre cell lymphoma in the EORTC classification spanned examples of follicular lymphoma and diffuse large B-cell lymphoma in the REAL and WHO classifications.[20] These discrepancies made meaningful comparison of studies on CBCL classified by either of these classifications impossible. Moreover, it resulted in considerable confusion on the biological behaviour and therapeutic approach in those lymphomas. The debate on CBCL was one of the driving forces to develop a new classification.

In several meetings in Lyon in 2003 and in Zürich in 2004 lymphoma experts adhering to the WHO classification and representatives of the EORTC cutaneous lymphoma group attempted to find agreement on the definitions and diagnostic criteria of CL. The WHO/EORTC classification for CLs represented the result of this consensus (Table 1).[7,8] It was the first classification for CL to be widely accepted by pathologists, dermatopathologists and dermatologists. As titled by Slater,[21] the WHO/EORTC classification represented a practical marriage of two professional giants. As regards the group of mature T-cell and natural killer (NK)/T-cell neoplasms, there were mostly minor differences and changes to the EORTC classification and WHO classification (3rd edn, 2001). The most significant changes in the WHO/EORTC classifications related to the definitions of CBCL (Table 1).

The current WHO classification (4th edn), published in 2008, is the result of a periodical update.[9] It adopted all entities of CL that were listed in the WHO/EORTC classification and integrated them into a general classification of nodal and extranodal lymphoid tumours with only minor changes in terminology (Table 1). As with the preceding classifications, it is based on a multiparameter approach. The WHO/EORTC classification and the recent WHO classification (4th edn) are accepted world-wide by pathologists, dermatopathologists, dermatologists and oncologists. By fulfilling these requirements, the terminology and disease definitions of the WHO classification are an important prerequisite for clinical studies, especially in multicentre trials and comparative studies.

Cutaneous lymphomas – nosological entities

The following section describes the clinicopathological features, definitions and diagnostic criteria of the CL entities as they are identified by the WHO/EORTC classification and the WHO classification (4th edn).

CUTANEOUS T-CELL LYMPHOMAS

In contrast to nodal lymphomas, in which B-cell NHLs represent the vast majority of lymphoid neoplasms, CTCL accounts for 65% of primary CL.[22] CTCL displays a broad spectrum of clinical manifestations with patches, plaques, papules and nodules.

Mycosis fungoides (MF) is the most common form of primary CL and makes up approximately 40% of all CL. In the WHO/EORTC and the WHO classification, the term MF is by definition restricted to classical cases with patches and plaques, or to variants showing a similar course. The so called d'emblée form of MF has been excluded and belongs to the group of primary cutaneous peripheral T-cell lymphoma, unspecified. Histologically, MF is characterized in its plaque stage by a dense, often band-like superficial infiltrate of small lymphocytes with atypical cerebriform nuclei, which is often accompanied by a variable number of eosinophils and occasionally by plasma cells. The epidermotropism of atypical lymphocytes with formation of Pautrier collections composed of atypical lymphocytes is the histological hallmark. In the early patch stage of MF, however, histological findings are subtle, with less prominent or even lacking atypia of lymphocytes, interface changes with vacuolization, and lining up of lymphocytes along the junctional zone. In early MF, epidermotropism with Pautrier collections is found in only 19% of biopsy specimens.[23] MF is a neoplasm of

Table 1. WHO/EORTC classification of cutaneous lymphomas

WHO/EORTC classification of cutaneous lymphomas	WHO classification for lymphoid tissues† (ICD-O Code)
Cutaneous T-cell and NK-cell lymphomas	Mature T-cell and NK-cell neoplasms
Mycosis fungoides (MF)	Mycosis fungoides (MF) (9700/3)
MF variants and subtypes	MF variants and subtypes
Folliculotropic MF	Folliculotropic MF
Pagetoid reticulosis	Pagetoid reticulosis
Granulomatous slack skin	Granulomatous slack skin
Sézary syndrome	Sézary syndrome (9701/3)
Adult T-cell leukaemia/lymphoma	Adult T-cell leukaemia/lymphoma (9827/3)
Primary cutaneous CD30+ lymphoproliferative disorders	Primary cutaneous CD30+ T-cell lymphoproliferative disorders
Primary cutaneous anaplastic large cell lymphoma	Primary cutaneous anaplastic large cell lymphoma (9718/3)
Lymphomatoid papulosis	Lymphomatoid papulosis (9718/1)
Subcutaneous panniculitis-like T-cell lymphoma*	Subcutaneous panniculitis-like T-cell lymphoma* (9708/3)
Extranodal NK/T-cell lymphoma, nasal type	Extranodal NK/T-cell lymphoma, nasal type (9719/3)
Primary cutaneous peripheral T-cell lymphoma, unspecified	Primary cutaneous peripheral T-cell lymphoma, rare subtypes
Primary cutaneous aggressive epidermotropic CD8+ T-cell lymphoma (provisional)	Primary cutaneous CD8+ aggressive epidermotropic cytotoxic T-cell lymphoma (provisional) (9709/3)
Cutaneous γ/δ+ T-cell lymphoma (provisional)	Primary cutaneous γ/δ T-cell lymphoma (9726/3)‡
Primary cutaneous CD4+ small/medium-sized pleomorphic T-cell lymphoma (provisional)	Primary cutaneous CD4+ small/medium T-cell lymphoma (provisional) (9709/3)
Cutaneous B-cell lymphomas	Mature B-cell neoplasms
Primary cutaneous marginal zone B-cell lymphoma	Extranodal marginal zone lymphoma of mucosa-associated lymphoid tissue (MALT lymphoma) (9699/3)
Primary cutaneous immunocytoma	
Primary cutaneous plasmacytoma	
Follicular hyperplasia with monotypic plasma cells	
Primary cutaneous follicle centre lymphoma	Primary cutaneous follicle centre lymphoma (9597/3)
Growth patterns: follicular, follicular and diffuse, diffuse	Diffuse large B-cell lymphoma, NOS (9680/3)
Primary cutaneous diffuse large B-cell lymphoma, leg type	Primary cutaneous diffuse large B-cell lymphoma, leg type (9680/3)
Primary cutaneous diffuse large B-cell lymphoma, other	Intravascular large B-cell lymphoma (9712/3)
Primary cutaneous intravascular large B-cell lymphoma	
Precursor haematological neoplasm	Precursor neoplasms
CD4+/CD56+ haematodermic neoplasm (formerly blastic NK cell lymphoma)	Blastic plasmacytoid dendritic cell neoplasm (9727/3)

*Phenotype (by definition): T-cell receptor α/β chain positive.
†List restricted to cutaneous lymphomas in the WHO classification (4th edn).
‡Provisional International Classification of Diseases (ICD)-O Code.

lymphoid cells with a CD4+ T-helper phenotype and a TH_2 cytokine pattern. Recently, various phenotypes of otherwise classic MF has been described including CD8+ MF, which often presents with hyper- or hypopigmented patches and plaques, CD56+ MF and CD4− CD8− double-negative MF.[24,25] These phenotypes do not appear to be of prognostic impact.[26] A T-cell clone is found in only half of biopsy specimens in early disease stages. Thus, neither molecular tests for T-cell clonality nor phenotypic markers are of significant diagnostic value in early MF.

MF displays a broad spectrum of variants and subtypes.[24] Folliculotropic MF is of importance due to its prognostic impact, since it exhibits a worse prognosis, with 5-year survival rates of approximately 60–70%, and thus requires more intensive treatment. The previously used term MF-associated follicular mucinosis has been replaced by folliculotropic MF, after two larger studies showed that not all folliculotropic MF cases were associated with mucinous degeneration of the hair follicles.[27,28] Similarly, the prognosis of granulomatous MF with a 5-year survival of 66% is

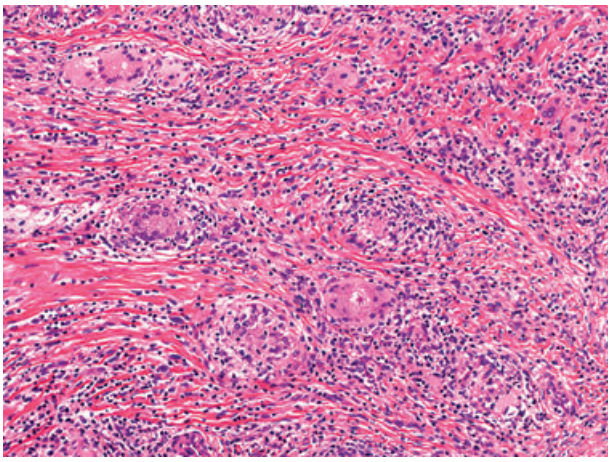

Figure 1. Granulomatous mycosis fungoides with multinucleated giant cells and small lymphocytes.

worse than in classic MF and in granulomatous slack skin (GSS).[29] Histologically, granulomatous MF presents with sarcoid-like or granuloma annulare-like infiltrates (Figure 1). Remarkably, epidermotropism of atypical lymphocytes is present in only half of cases.[29] Since granulomatous MF and GSS exhibit overlapping and often identical histological features, the distinction between granulomatous MF and GSS is based on the clinical manifestation with occurrence of bulky skin folds in the intertriginous areas in GSS.[29] Pagetoid reticulosis and GSS were listed as subtypes of MF mainly due to their distinct clinical features and excellent prognosis. Pagetoid reticulosis is by definition restricted to cases with a well-circumscribed erythematous and scaling, slowly growing solitary lesion. Histologically, there is prominent epidermotropism of small and medium-sized lymphocytes with cytoplasmic halo and variable phenotypes including CD4+, CD8+ and CD30+ forms.[30] Recently, recommendations for the stage-adapted treatment of MF have been published.[31] Ultraviolet-light therapy and retinoids are therapeutic cornerstones in patch and plaque stages of the disease.

Sézary syndrome (SS) is a rare form of CTCL, accounting for 3% of all CLs. The characteristic clinical presentation encompasses erythroderma, alopecia, palmoplantar hyperkeratosis and lymphadenopathies.[32] Histologically specific features with epidermotropism of atypical lymphocytes are found in only 40% of biopsy specimens, which makes the histological assessment of SS challenging.[33] In the remaining cases, a band-like infiltrate of small lymphocytes with or without nuclear atypia and lack of epidermotropism or only a subtle perivascular infiltrate are found.[33–35] There is leukaemic spread of tumour cells with atypical enlarged lymphocytes, so called Sézary or Lutzner cells. In most definitions, >1000 cerebriform cells/ml peripheral blood are required for the diagnosis of SS, but consensus on the diagnostic criteria for SS has still to be found.[36] The prognosis of SS is poor, with a median survival of 2–4 years.[6]

The primary cutaneous CD30+ lymphoproliferative disorders (LPD) are the second most common from of CTCL.[37] This group represents a spectrum of diseases including lymphomatoid papulosis (LyP), primary cutaneous anaplastic large cell lymphoma (PCALCL) and borderline cases. LyP is characterized by multiple papulo-nodular lesions (Figure 2), which undergo spontaneous regression after a few weeks or months. The disease usually persists for years or even decades, but has an excellent prognosis.[38] Aggressive treatment should thus be avoided. Nevertheless, patients suffering from LyP should be monitored life-long, since 5–25% of patients develop a second lymphoma like Hodgkin's lymphoma, MF and primary cutaneous or nodal anaplastic large cell lymphoma (ALCL).[38] The expression of fascin may represent a prognostic marker indicating increased risk for the development of second lymphomas in LyP patients.[39] Histologically, LyP exhibits a spectrum ranging from scattered or grouped CD30+ large pleomorphic or anaplastic tumour cells in the background of neutrophils and eosinophils (type A) (Figure 3A,B) to an epidermotropic infiltrate of small lymphocytes (type B) or cohesive sheets of tumour cells with only a few admixed reactive cells (type C).[40] The CD30+ cells in LyP express CD4 and commonly T-cell intracytoplasmic antigen-1 (TIA-1), but other phenotypes (CD8+ or CD56+) are also observed. Tumour necrosis factor receptor-associated factor-1 (TRAF-1) and MUM1 have recently been described as adjunctive

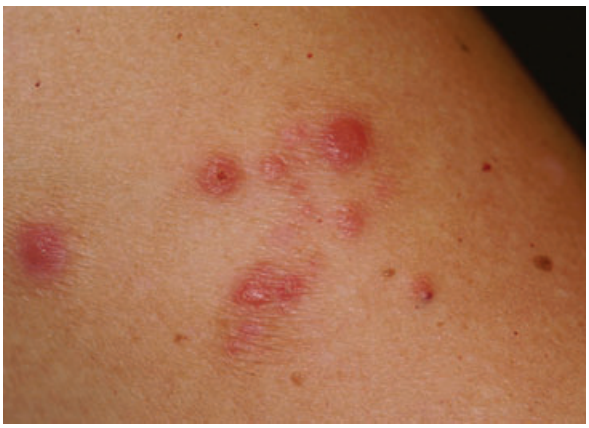

Figure 2. Lymphomatoid papulosis with grouped papules. One lesion shows a small central ulceration.

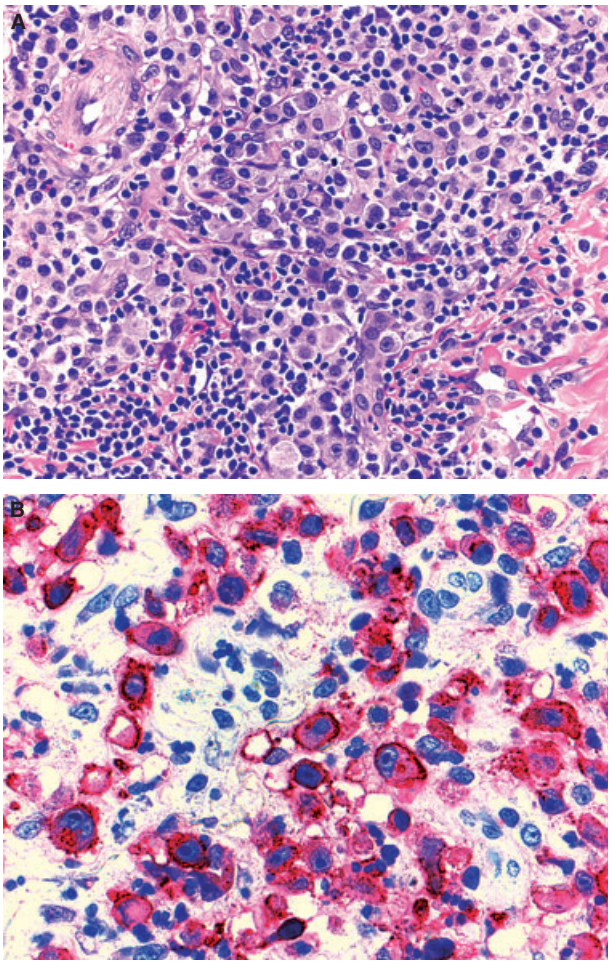

Figure 3. Lymphomatoid papulosis. A, Large anaplastic tumour cells, small lymphocytes and eosinophils. B, Expression of CD30 by the tumour cells.

markers for differentiating between LyP and PCALCL, but contradictory results on their diagnostic value have been reported.[41–43] LyP, PCALCL and secondary infiltrates of systemic ALCL as well as tumour stage of MF and transformation in SS show overlapping histological and phenotypical features and may be impossible to distinguish on histological and phenotypic grounds alone. It exemplifies that differentiation can be achieved only by clinicopathological correlation and staging examinations.

In contrast to LyP, PCALCL presents with solitary or grouped, frequently ulcerated large tumours. Histologically, a nodular cohesive infiltrate of large pleomorphic, anaplastic or immunoblastic tumour cells with a high mitotic rate is found. Eosinophils may be admixed.[44] By definition, >75% of the tumour cells have to express CD30.[7,37] The tumour cells most commonly express CD4, but CD3 expression may be weak or absent. In contrast to systemic ALCL, which frequently shows expression of ALK due to underlying t(2;5) translocation, PCALCL lacks this transformation and expression of ALK in the vast majority of cases.[45,46] The neutrophil-rich form of ALCL shows scattered tumour cells within dense infiltrates of neutrophils and may simulate pyoderma gangrenosum.[47] The prognosis of PCALCL is favourable, with a 5-year survival rate of 95%, even in patients with involvement of regional lymph nodes.[38] Excision and radiotherapy are first-line therapy in solitary tumours. Low-dose methotrexate is effective for grouped or multiple lesions of PCALCL. Multiagent chemotherapy should be restricted to cases with extracutaneous spread.[38]

Subcutaneous panniculitis-like T-cell lymphoma (SPTCL) accounts for 1% of all CL. In the WHO/EORTC classification and the WHO classification (4th edn, 2008), this term is by definition restricted to cases expressing a T-cell receptor (TCR) α/β phenotype.[7,9] The demonstration of expression of β-F1 (TCR α/β) by immunohistochemistry is a pivotal diagnostic marker for this entity, which accounts for 75% of all subcutaneous forms of T-cell lymphomas. Histologically, lobular infiltrates of small to medium-sized lymphoid cells with pleomorphic nuclei are found. Karyorrhexis and cytophagocytosis may be present (Figure 4). There is rimming of adipocytes by tumour cells, but this is not an entirely disease-specific feature. It can also be seen in lupus panniculitis, which is one of the major differential diagnoses. Phenotypically, SPTCL expresses CD8 and cytotoxic proteins. SPTCL is associated with a good prognosis with a 5-year survival rate of 80%.[48]

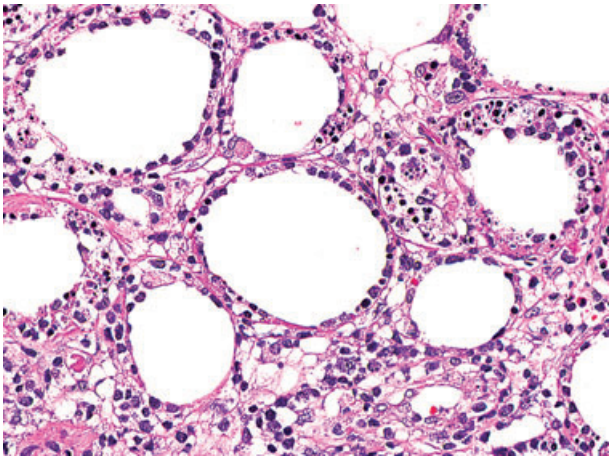

Figure 4. Subcutaneous panniculitis-like T-cell lymphoma: infiltrates of small and medium-sized lymphoid cells with pleomorphic nuclei. Rimming of adipocytes by tumour cells, karyorrhexis and cytophagocytosis.

Tumour spread to other tissues is rare. In contrast, tumour cells in subcutaneous lymphoma with a γ/δ TCR phenotype express CD56, CD2 and CD3, but are negative for CD4 and CD8. Immunohistochemically the γ/δ TCR phenotype can be demonstrated by expression of TCR δ-1 (TCR γ/δ) on fresh frozen tissue or indirectly by the lack of β-F1 expression on formalin-fixed paraffin-embedded biopsy specimens. Histologically, angiocentric growth may be found. Often additional involvement of the dermis and even an epidermotropic component of the infiltrate is seen. In contrast to the TCR α/β+ form, the γ/δ+ form has an unfavourable prognosis.[48,49] Cases displaying a TCR γ/δ phenotype were therefore excluded from subcutaneous panniculitis-like T-cell lymphoma and reclassified as part of primary cutaneous γ/δ T-cell lymphoma.[48] Whereas α/β+ SPTCL can be controlled by systemic steroids or even followed by a 'wait and see' strategy, γ/δ+ lymphoma with subcutaneous involvement requires multiagent chemotherapy, new targeted therapies or even allogeneic bone marrow stem cell transplantation.

All cases that do not belong to MF, SS, CD30+ LPD, SPTCL or extranodal NK/T-cell lymphoma are assigned to the group of peripheral T-cell lymphoma, unspecified (PTL, NOS) according to the WHO/EORTC and WHO classifications. This still poorly characterized entity most often presents with rapidly evolving multiple nodules without preceding patches and plaques as in MF.[50] By definition, CD30 expression is absent or limited to only a minority of tumour cells. Among PTL, NOS, three subtypes with distinct clinical and pathological and prognostic features were delineated. Cutaneous γ/δ lymphomas have been listed a provisional entity in the WHO/EORTC classification and have been incorporated as a separate entity in the WHO classification (4th edn, 2008). This lymphoma is rare.[49] Involvement of the subcutis and epidermotropic infiltrates and angiocentric and angiodestructive growth are frequently observed.[51] The tumour cells express CD2, CD3, CD56 and cytotoxic proteins, but are negative for Epstein–Barr virus in most cases. Prognosis is poor independent of primary or secondary cutaneous involvement. Treatment with multiagent chemotherapy and bone marrow transplantation may be effective.

Primary cutaneous aggressive (epidermotropic) CD8+ T-cell lymphoma (CD8+ AETCL) represents another subtype of PTL, NOS, associated with a poor prognosis and a median survival time of <3 years.[49,52] This lymphoma presents with disseminated, rapidly evolving erosive or ulcerating plaques and nodules. Histology shows an epidermotropic infiltrate of small to medium-sized lymphoid cells with pleomorphic nuclei and numerous necrotic keratinocytes, erosion and ulceration (Figure 5). The tumour cells express CD8, TIA-1 and other cytotoxic proteins and CD45RA. This subtype of PTL, NOS has to be distinguished from CD8+ MF, which also displays a band-like and epidermotropic infiltrate, but only very few or no necrotic keratinocytes. In contrast to CD8+ AETCL, CD8+ MF manifests clinically with hyper- or hypopigmented patches and plaques, but no erosions, necroses or ulcerations, and has the same favourable prognosis as classic MF.

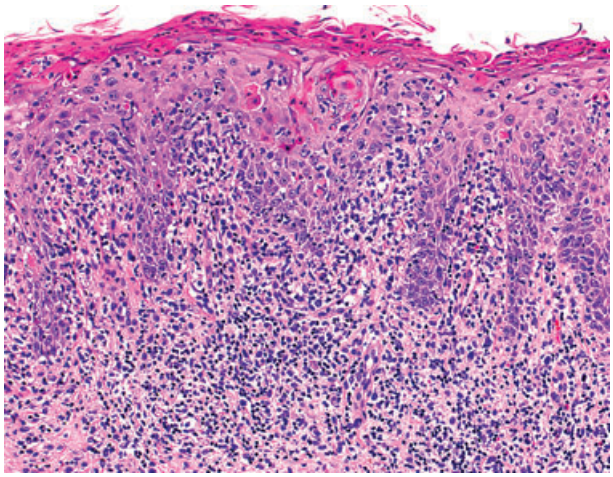

Figure 5. Primary cutaneous aggressive epidermotropic CD8+ cytotoxic T-cell lymphoma: epidermotropism of small to medium-sized tumour cells with atypical, chromatin dense nuclei. Note the numerous necrotic keratinocytes.

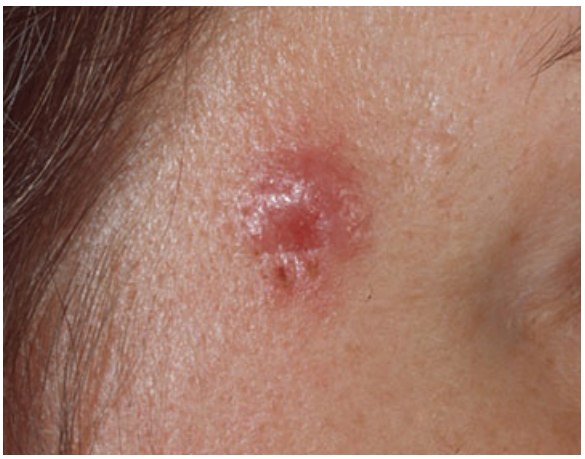

Figure 6. Primary cutaneous CD4+ small/medium-sized pleomorphic T-cell lymphoma: nodular lesion on the face.

The primary cutaneous CD4+ small/medium pleomorphic T-cell lymphoma (CD4+ SMPTL) is a provisional entity within the group of PTL, NOS. It presents in most cases with a solitary nodule in the absence of

preceding patches and plaques (Figure 6).[53] Histologically, nodular infiltrates of small or to a lesser extent medium-sized slightly pleomorphic lymphocytes and admixed eosinophils, plasma cells and histiocytes are found.[54] Epidermotropism may focally be present. Distinction from nodular form of T-cell pseudolymphoma (PSL) is challenging. Nuclear pleomorphism and detection of a clonal T-cell population favour the diagnosis of CD4+ small/medium T-cell lymphoma. Recent studies indicate that this entity in fact represent a neoplastic proliferation of follicular T-helper cells based on the expression of CXCL-13 and PD-1.[55] CD4+ SMPTL exhibits a favourable prognosis with 5-year survival rates of >90%,[50] but recent data suggest that this CL entity may encompass a prognostically heterogeneous group of tumours.[56]

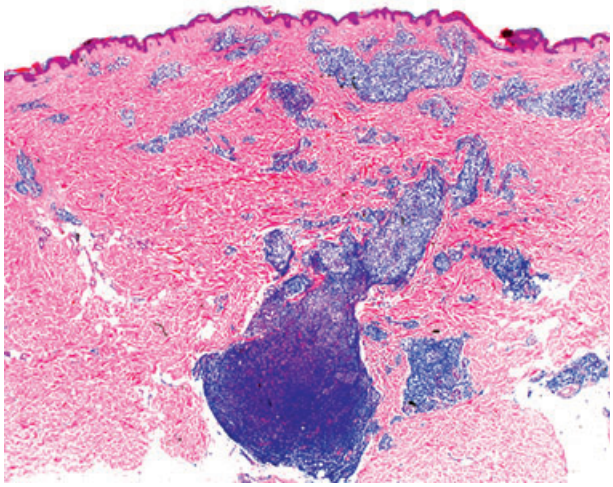

Figure 7. Primary cutaneous marginal zone B-cell lymphoma (MALT lymphoma): nodular and confluent infiltrates of small lymphocytes (darker areas) with remnants of germinal centres (pale zones).

CUTANEOUS B-CELL LYMPHOMAS

The classifications of CBCL has long been a matter of confusion and debate. It is therefore not surprising that the most significant changes in the WHO/EORTC classifications belonged to CBCL. The WHO classification (4th edn, 2008) has adopted the definitions and criteria of the WHO/EORTC classification (Table 1).

Primary cutaneous marginal zone B-cell lymphoma (PCMZL) is defined as an indolent B-cell lymphoma composed of small B cells, marginal zone cells, lymphoplasmacytoid cells and mature plasma cells.[7,57] In the WHO classification (4th edn, 2008), PCMZL belongs to the group of extranodal marginal zone lymphoma of MALT lymphoma.[58] Recent data suggest that most cases of PCMZL differ from other extranodal marginal zone lymphomas as regards the expression of class-switched immunoglobulins and CXCR3.[59] As regards classification, histological and immunophenotypic similarities nevertheless justify including PCMZL in the larger group of extranodal MALT lymphomas. Histologically, nodular and confluent infiltrates of small lymphocytes, mostly lymphoplasmacytoid cells or more rarely monocytoid cells, are the major component of PCMZL (Figure 7). These cells express B-cell markers and Bcl-2, but are negative for Bcl-6. The infiltrates are separated from the overlying epidermis by a Grenz zone.[60] Additionally, reactive germinal centres of varying number and size and numerous T cells as well as histiocytes are commonly found in PCMZL. Monotypic plasma cells are mostly located at the periphery of the infiltrates and are a major diagnostic criterion for MZL, but there is no consensus on the ratio of immunoglobulin light chains required to be monotypic. Differentiation from other B-cell infiltrates with follicular pattern can be challenging.

Absence of mantle zone and lack of polarization were identified as distinguishing features in PCFCL,[61] but diagnosis can be achieved only by correlating clinical, histological, phenotypic features and clonality data. Recent data showed clusters of CD123+ plasmacytoid dendritic cells (PDC) in all cases of PCMZL, but not in other forms of CBCL. Thus, PDC may be a diagnostic marker for differentiation from other CBCLs, but they do not distinguish PCMZL from B-cell PSL.[62] PCMZL has an excellent prognosis, with a 5-year survival rate of 98%, but recurrences are seen in half of patients.[63,64] Extracutaneous spread occurs very rarely. Excision and radiotherapy are first-line therapies.[65] Alternatively, intralesional interferon-alpha and intralesional or systemic rituximab are effective.[66] The aetiopathogenesis of PCMZL has still to be elucidated. The similarities between PCMZL and B-cell PSL and the link with other extranodal MALT lymphomas suggest that PCMZL is a lymphoproliferation driven by infectious agent(s) or autoantigens. In a subset of cases, borrelia species and hepatitis C virus sequences could be found, but they may be only two out of several infectious agents linked to PCMZL.[67,68] The findings of PDC and T cells in B-cell PSL and PCMZL indicate that these two diseases may represent different evolutionary steps of a lymphoproliferation composed of PDC, T cells and B cells driven by antigenic stimulation.[69]

Primary cutaneous follicle centre lymphoma (PCFCL) is defined as a tumour of neoplastic follicle centre cells with a mixture of small and large cleaved cells (centrocytes) and, to a lesser extent, large non-cleaved cells (centroblasts) with prominent nucleoli.[7,8] In the WHO classification (4th edn, 2008), PCFCL is listed as a

separate entity and not only as a variant of extranodal follicular lymphomas.[9] Histologically, three growth patterns can be seen: a follicular, a follicular and diffuse, and a diffuse pattern. In all three patterns, the tumour is predominantly composed of centrocyte-like tumour cells with cleaved nuclei. In the follicular growth pattern, the tumour cells are arranged in large neoplastic follicles, which lack polarization and display a small or absent mantle zone.[70] Tingible body macrophages are usually not present.[61] The diffuse pattern is in fact the most common seen in PCFCL. No follicular structures can be discerned, but irregular networks of CD21+ follicular dendritic cells are found and may be an adjunctive maker for differentiation between this growth pattern of FCL and the diffuse infiltrates in DLBCL, leg type. The tumour cells in PCFCL express CD20 and Bcl-6. In contrast to nodal FCL, Bcl-2 expression and t(14;18) are found in only a small minority of PCFCL. PCFCL has an excellent prognosis, with a 5-year survival rate of >90%.[6,64] Nevertheless, recurrences are seen in up to 40% of patients. Extracutaneous spread occurs very rarely. PCFCL arising at the legs and those cases with expression of FOX-P1 appear to have a worse prognosis and should probably be treated more aggressively, similar to DLBCL, leg type.[71]

In contrast to these low-malignant CBCL forms, primary cutaneous diffuse large B-cell lymphoma (PCDLBCL) is characterized by a dense nodular infiltrate of centroblast-like and immunoblast-like tumour cells with non-cleaved nuclei and prominent nucleoli, but without significant admixture of centrocyte-like cells (Figure 8). Among the group of PCDLBCL, the most common form is PCDLCBL, leg type, which frequently develops on the legs of elderly patients and exhibits an unfavourable prognosis.[71,72] It may appear unusual to add the localization to the designation of this lymphoma entity. It is, however, paralleled by other extranodal lymphomas such as extranodal NK/T-cell lymphoma, nasal type. PCDLBCL, leg type displays a characteristic phenotype with strong expression of Bcl-2 and MUM1, but variable expression of Bcl-6 and absence of CD10.[72] Apart from the leg type of PCDLBCL, the plasmablastic lymphoma and the T-cell-rich large B-cell lymphoma were included into the group of DLBL. The term PCDLBCL, other, was used to designate diffuse B-cell lymphomas that lack the typical clinical, histological and phenotypic features of PCDLBL, leg type, and do not conform to the definition of PCFCL. These very rare cases show an intermediate prognosis.[73]

The blastic plasmacytoid dendritic cell neoplasm is rare, and has traditionally been included in lymphoma classifications. Its designations serve as an example of the evolution of the terms applied to this aggressive lymphoma. Originally considered as a blastic NK-cell lymphoma, expanding knowledge of dendritic cells and the immunophenotypic characterization of the tumour cells showed that the tumour cells belong to plasmacytoid dendritic cells.[74] Thus, the designations of the same entity underwent changes from blastic NK-cell lymphoma to agranular CD4+ CD56+ haematodermic neoplasm (WHO/EORTC classification 2005)[75] and finally blastic plasmacytoid dendritic cell neoplasm in the WHO classification.[76] The disease presents with multiple contusiform plaques. Involvement of oral mucosa is common. Histologically, there is a diffuse monotonous infiltrate, which is band-like in the upper

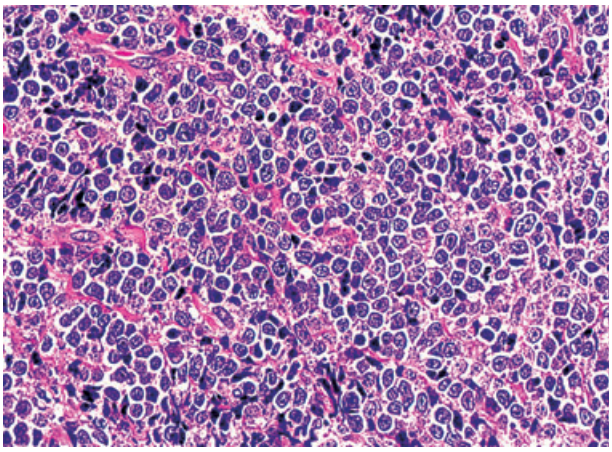

Figure 8. Primary cutaneous diffuse large B-cell lymphoma, leg type: infiltrate composed predominantly of centroblast-like and immunoblast-like tumour cells with round, non-cleaved nuclei and prominent nucleoli. Admixture of a few centrocyte-like cells with cleaved nuclei.

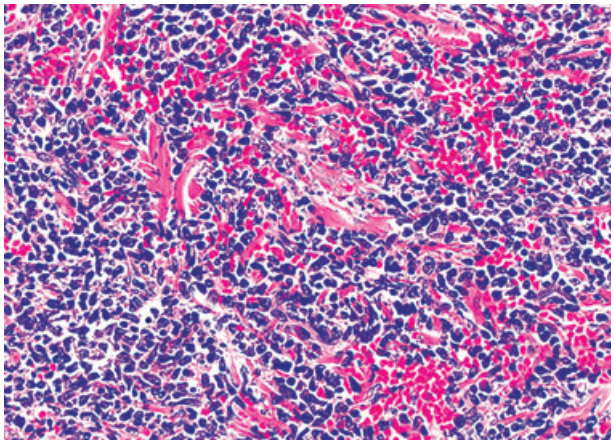

Figure 9. Blastic plasmacytoid dendritic cell neoplasm: tumour cells display nuclei with fine dispersed chromatin. Note extravasated erythrocytes.

and mid dermis with column-like extensions into the deeper dermis and subcutis. The tumour cells resemble blasts with fine dispersed chromatin (Figure 9). Numerous extravasated erythrocytes are found between the tumour cells, which give the lesions their characteristic clinical contusiform appearance. This neoplasm displays a unique phenotype with expression of CD4, CD56, CD123, and TCL-1.[74] In some patients, the disease develops in the context of myelodysplastic syndrome.[77] Leukaemic spread occurs in the majority of patients (70%).[74] This dendritic cell neoplasm is associated with a poor prognosis.[74,76]

Practical implications

A biopsy specimen of skin lesions assumed to represent CL is in most circumstances the starting point for the diagnostic work-up. The immunophenotype and genetic features of almost all forms of primary and secondary cutaneous lymphomas can today be determined in archival, i.e. formalin-fixed paraffin-embedded tissue. One has to be aware that both immunophenotyping and molecular techniques have their pitfalls. For example, atypically appearing CD30+ activated enlarged lymphocytes can be found in a variety of inflammatory disorders such as scabies, arthropod bite and drug reactions. Therefore, the mere detection of larger CD30+ cells in the background of neutrophils and eosinophils should not be equated with lymphomatoid papulosis.[78]

The multiparameter approach in the diagnosis of CL diseases has essential practical implications. The fundamental role of clinicopathological correlation to achieve final diagnosis in primary CL implies that the first pathology report provides in most cases a list of possible differential diagnoses rather than a definite diagnosis. Final diagnosis can be established only after results on staging examinations have been obtained and after the clinical manifestation of the disease has been assessed by direct skin examination or on clinical photographs of sufficient quality. The introduction of the widely accepted WHO/EORTC classification for CL and the WHO classification (4th edn, 2008) should prompt both clinicians and pathologists to refer in their diagnostic terminology only to these classifications. Thereby they avoid confusion, which would result from the use of divergent terminologies from previous classifications.

Since the TNM staging system as outlined in its sixth version (2002) did not sufficiently reflect the extent of cutaneous involvement (T stage),[79] new TNM staging schemes for MF, SS as well as for other CL have been proposed.[80,81] The applicability and reproducibility of these new staging schemes have been demonstrated in recent studies on a large number of CBCLs.[64,82] The future will show whether they will also find acceptance among oncologists and surgical pathologists. A matter of debate concerns the need for bone marrow aspirates in the staging work-up of patients with CL who do not show involvement of peripheral blood or extracutaneous sites in radiological staging examinations. Two recent studies have highlighted that involvement of bone marrow is an uncommon finding in PCALCL and in PCMZL.[83,84] The authors provide evidence that routine examination of bone marrow must no longer be recommended for these two entities.

The spectrum of CL is broad and complex. Furthermore, there is a rapidly increasing number of new and emerging therapies for various forms of CL. As a consequence of the complex classifications and the increasing therapeutic modalities, the diagnostic work-up and treatment of CL are recommended to be performed at specialized centres and by an expert panel including dermatologists, dermatopathologists and haematopathologists. Specialized units have been established at most academic medical institutions and serve as referral centres for patients with CL. They have a crucial role not only in establishing the diagnosis and the therapeutic approach, but also in exposing patients to clinical studies with new therapeutic approaches. The majority of CL patients suffer from slowly progressive and indolent forms of CL. None or only minimal therapeutic intervention in their initial disease stage is needed. Most patients will therefore alternately be treated in both private dermatological practice and the specialized centre in the setting of a close collaboration.

Future perspectives

Classifications of lymphomas are significantly influenced by the discovery of new diagnostic and prognostic markers and new cell types of the immune system. Clinicopathological studies on a series of well-characterized lymphomas are and will be of major impact in identifying further subsets of lymphoma entities with different biological behaviour and the necessity for a different therapeutic approach. Among others, the meetings of EORTC Histopathology Task Force for cutaneous lymphomas contribute to this goal, as recently shown for subcutaneous T-cell lymphomas and granulomatous CTCL.[29,48] The latter study showed that the prognosis of granulomatous MF with a 5-year survival of 66% is worse than in classic MF and GSS.[29] Similar to folliculotropic MF, granulomatous MF should therefore be included as a distinct variant of MF mainly due to its prognostic impact. In intravascular large

B-cell lymphoma, cases limited to the skin show a better prognosis.[85] Thus a cutaneous variant of this lymphoma entity may be explicitly added to an updated edition of the WHO classification. Further studies are needed to characterize in detail recently described neoplasms such as the indolent CD8+ lymphoid proliferation of the ear.[86]

Future classifications will provide updated diagnostic criteria. Therefore, one of the issues to be addressed and clarified in forthcoming classifications is diagnostic criteria for early stages of MF and for SS. Furthermore, criteria to separate primary cutaneous CD4+ SMPTL from T-cell PSL are needed. Future classification will most probably also contain recommendations for the panel of staging examinations and the documentation of disease stage, particularly since bone marrow biopsy is not any longer considered as essential for all forms of CL as outlined above.

Modern techniques for the detection of disease-specific or prognostically relevant genetic and epigenetic alterations contribute in a significant and increasing way to reclassification of CL. For example, fluorescence *in situ* hybridization analysis for the detection of lymphoma-associated chromosomal abnormalities can today be performed on archival, i.e. formalin-fixed paraffin-embedded tissue.[87] In nodal lymphomas, detection of these abnormalities was shown to be of diagnostic value. Recent studies indicate the occurrence of disease-specific alterations also in CL.[88] In future, molecular profiling by RNA or DNA microarrays will most probably be applied in a similar manner as immunophenotyping or polymerase chain reaction are used today in the diagnostic work-up of CL.[89] Most of these genetic alterations and profiles will not be entirely disease specific and will probably not be restricted exclusively to one lymphoma entity. Thus, the results obtained from molecular genetic examinations will also have to be interpreted in the context of clinical, histological and immunophenotypic features. Subtle differences in the protocols underlying immunophenotypic and genetic profiling may result in significantly divergent results obtained by different laboratories and investigators. For example, recent studies investigating the expression of MUM1 and TRAF1 in cutaneous CD30+ LPD used different antigen retrieval protocols, which led to contradictory results.[41–43] Tests for diagnostic and prognostic markers should therefore be standardized. The introduction of the BIOMED 2 protocols for T- and B-cell clonality represents the result of a consensus on such standards in molecular techniques.[90]

The identification of new types or subsets of immune cells will have impact on the classification of nodal and cutaneous lymphomas. Recent studies showed that tumour cells in angioimmunoblastic T-cell lymphoma and peripheral T-cell lymphoma, follicular type, belong to follicular helper T cells based on their expression of CXCL13 and PD-1.[91] In CL, expression of these markers by the tumour cell population has been found in primary cutaneous CD4+ SMPTL.[55] Such findings may prompt the reclassification of certain CTCL subtypes.

From a practical point, training of oncologists, haemato-oncologists, dermatopathologists and pathologists in the principles and practical application of current and future classifications is crucial to ensure broad acceptance of the classification and to facilitate communication.

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