WHO/EORTC classification of cutaneous lymphomas 2005: histological and molecular aspects

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Abstract: The new WHO/EORTC classification for cutaneous lymphomas comprises mature T-cell and natural killer (NK)-cell neoplasms, mature B-cell neoplasms, and immature hematopoietic malignancies. It reflects the unique features of lymphoproliferative diseases of the skin, and at the same time it is as compatible as possible with the concepts underlying the WHO classification for nodal lymphomas and the EORTC classification of cutaneous lymphomas. This article reviews the histological, phenotypical, and molecular genetic features of the various nosological entities included in this new classification. These findings always have to be interpreted in the context of the clinical features and biologic behavior.

Aim: To review the histological, phenotypical and molecular genetic features of the various nosological entities of the new WHO/EORTC classification for cutaneous lymphomas.

Methods: Extensive review of the literature cited in Medline and own data of the authors.

Results: The WHO/EORTC classification of cutaneous lymphomas comprises mature T-cell and NK-cell neoplasms, mature B-cell neoplasms and immature hematopoietic malignancies. It reflects the unique features of primary cutaneous lymphoproliferative diseases.

Conclusion: This classification is as much as possible compatible with the concept of the WHO classification for nodal lymphomas and the EORTC classification of cutaneous lymphomas. The histological, phenotypical and molecular genetic features always have to be interpreted in the context of the clinical features and biologic behavior.

Burg G, Kempf W, Cozzio A, Feit J, Willemze R, Jaffe ES, Dummer R, Berti E, Cerroni L, Chimenti S, Diaz-Perez JL, Grange F, Harris NL, Kazakov DV, Kerl H, Kurrer M, Knobler R, Meijer CJLM, Pimpinelli N, Ralfkiaer E, Russell-Jones R, Sander C, Santucci M, Sterry W, Swerdlow SH, Vermeer MH, Wechsler J, Whittaker S. WHO/EORTC classification of cutaneous lymphomas 2005: histological and molecular aspects.
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Over the past 50 years, the classification of lymphomas has been a source of controversy, both for those studying primarily nodal disease and those interested in cutaneous lymphomas, as well as an area of interdisciplinary disagreement. There never will be a classification for lymphomas that can cover the broad spectrum of nodal and extranodal lymphomas at the same time and fully reflect the many organ-specific biological peculiarities. Nevertheless, one basic terminology should be used for both nodal and extranodal lymphomas.

During two consensus meetings in Lyon, France in September 2003 and in Zürich, Switzerland in January 2004 and in many additional discussions, a group of pathologists and dermatologists elaborated the WHO/EORTC classification for primary lymphoproliferative disorders (LPD) of the skin[1–4] which reflects the specific features of cutaneous lymphomas. The WHO/EORTC classification has been developed on the base of the EORTC classification for cutaneous lymphomas[5] and the WHO classification for nodal lymphomas[6] and respects the framework of the basic WHO classification for nodal lymphomas.[7]

The clinical aspects of the new classification recently have been reviewed.[2] This article focuses on the histological and molecular findings in the various disease entities with special reference to the differences between nodal and cutaneous lymphomas.

WHO/EORTC classification for cutaneous lymphomas

The distinct histological, phenotypic, and molecular biological features of the entities listed in the new WHO/EORTC classification for cutaneous lymphomas (Table 1)[1,2,4] are presented.

Cutaneous T-cell lymphomas

Mycosis fungoides (MF)

Mycosis fungoides (MF), the prototype of cutaneous T-cell lymphomas (CTCL), accounts for approximately 44% CL.[2] MF initially presents in the skin and shows a characteristic stepwise clinical progression with potential extracutaneous involvement.

Synonyms in other classifications

WHO/EORTC classification (2005): mycosis fungoides
WHO classification (2001): mycosis fungoides
REAL classification (1997): mycosis fungoides
EORTC classification (1997): mycosis fungoides

Clinical features

The disease starts with patches, which after years or even decades develop into thin and thick plaques. In a minority of patients, the disease results eventually in tumors and in dissemination to lymph nodes, blood,

Table 1. The WHO/EORTC classification for cutaneous lymphomas[1–3]

Mature T-cell and NK-cell neoplasms

Mycosis fungoides (MF)
Variants of MF
  Pagetoid reticulosis (localized disease)
  Folliculotropic, syringotropic, granulomatous variants
Subtype of MF
  Granulomatous slack skin

Sézary syndrome

$CD30^+$ T-cell lymphoproliferative disorders of the skin
  Lymphomatoid papulosis
  Primary cutaneous anaplastic large cell lymphoma

*Subcutaneous panniculitis-like T-cell lymphoma**

Primary cutaneous peripheral T-Cell lymphoma (PTL), unspecified
Subtypes of PTL
  Primary cutaneous aggressive epidermotropic $CD8^+$ T-cell lymphoma (provisional)
  Cutaneous gamma/delta-positive T-cell lymphoma (provisional)
  Primary cutaneous $CD4^+$ small/medium-sized pleomorphic T-cell lymphoma (provisional)

Extranodal NK/T-cell lymphoma, nasal type†
  Hydroa vacciniforme-like lymphoma (variant)

Adult T-cell leukemia/lymphoma†

Angioimmunoblastic T-cell lymphoma†

Mature B-cell neoplasms

Cutaneous marginal zone B-cell lymphoma (MALT-type)

Primary cutaneous follicle center lymphoma
Growth patterns
  Follicular
  Follicular and diffuse
  Diffuse

Cutaneous diffuse large B-cell lymphoma, leg type

Cutaneous diffuse large B-cell lymphoma, others

Intravascular large B-cell lymphoma†

Lymphomatoid granulomatosis†

Chronic lymphocytic leukemia†

Mantle cell lymphoma†

Burkitt lymphoma†

Immature hematopoietic malignancies

Blastic NK-cell lymphoma‡ *$CD4^+$/$CD56^+$ hematodermic neoplasm*

Precursor lymphoblastic leukemia/lymphoma†
  T-lymphoblastic lymphoma†
  B-lymphoblastic lymphoma†

Myeloid and monocytic leukemias†

Hodgkin lymphoma

*Definition is restricted to lymphomas of alpha/beta T-cell origin.
†This table also contains entities of extracutaneous lymphomas frequently involving the skin as a secondary site.
‡Recent evidence suggests an origin from a dendritic cell precursor. In recognition of uncertain histogenesis the term $CD4^+$/$CD56^+$ hematodermic neoplasm is preferred.

bone marrow, and internal organs. Involvement of mucous membranes is an exception. The disease does not develop continuously, but instead shows a stepwise progression, suggesting that the steps reflect cumulative mutations in various genes involved in the pathogenesis of the neoplastic process.[8,9]

Histology

The histologic diagnosis of early MF usually is difficult to establish, as the disease may closely resemble dermatitis in its early stages.[10] The most specific finding, seen in only 10% of lesions, are Pautrier microabscesses (Fig. 1A). The presence of medium-to-large hyper-convoluted cerebriform cells in the epidermis larger than dermal lymphocytes, showing a clear perinuclear halo (haloed lymphocytes), or lymphocytes in clusters in the dermis, and lymphocytes aligned within the basal layer are typical but not specific features.[11] In early MF, presence of lymphocytes with strikingly irregular nuclear contour and/or variable nuclear and cytoplasmic features is of diagnostic value with a sensitivity of 53.3% and a specificity of 88.9%[12]. There usually is little spongiosis. A study analyzing 745 biopsy specimens of early MF[13] demonstrated that epidermotropism of lymphocytes was almost always present, but missing in 4% of cases. The combination of a patchy band-like infiltrate and elongated,

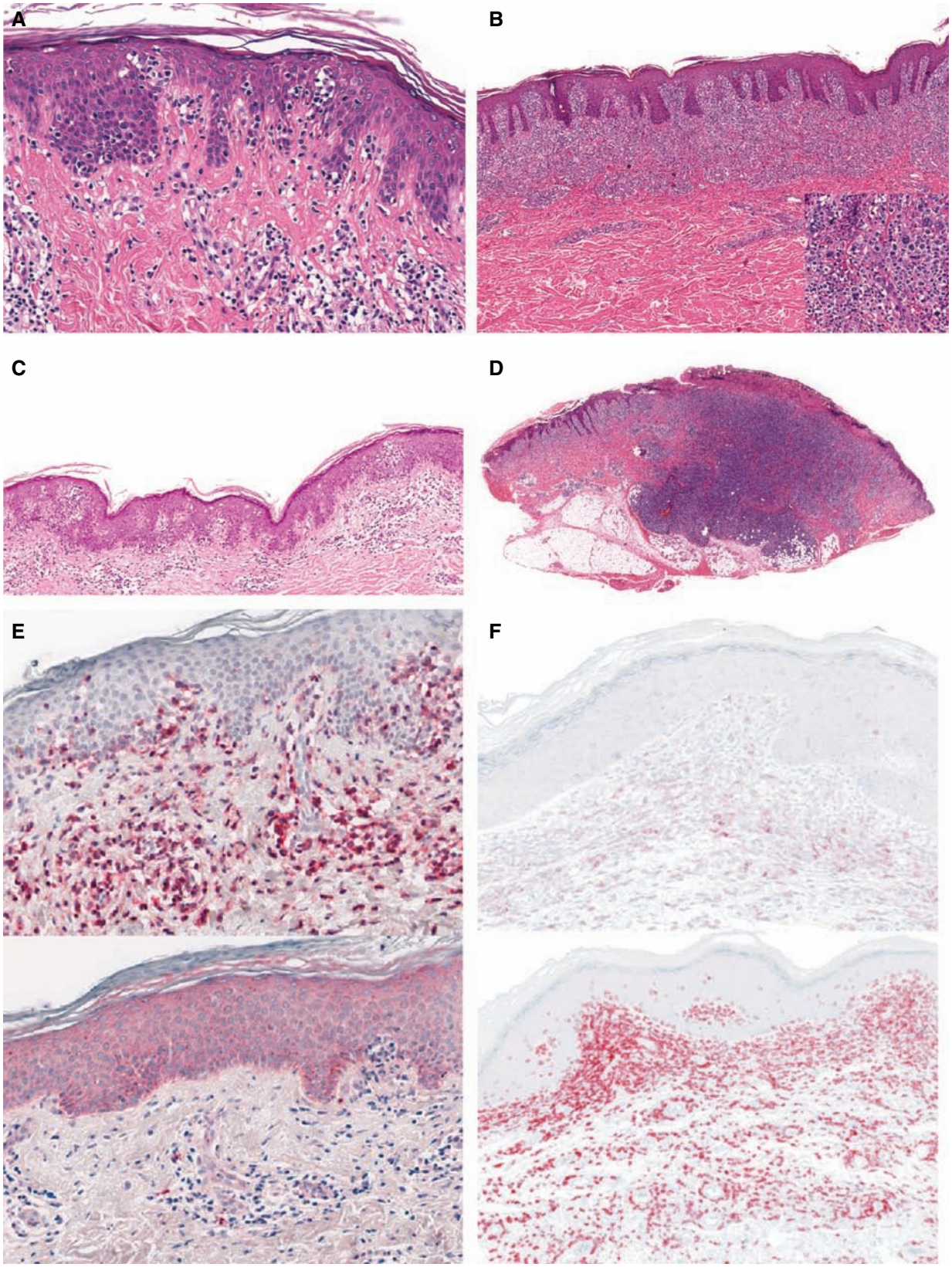

Fig. 1. A) Patch stage of mycosis fungoides (MF): epidermotropic lymphocytic infiltrate forming Pautrier microabscesses; intraepidermal atypia of the intraepidermal lymphocytes. B) Early stage of MF: superficial perivascular lymphocytic infiltrate with epidermotropism along the basal layer (lining up) and in upper levels of the epidermis. C) Plaque stage of MF: dense band-like lymphoid infiltrate with epidermotropism. Inset: dense infiltrate of atypical lymphocytes. D) MF in transformation: dense lymphocytic infiltrate reaching deep into the subcutaneous fat and ulceration. E) Plaque stage of MF: predominance of CD4 (top) over CD8 cells (bottom). F) $CD8^+$ MF: The cells are $CD4^-$ (top) and $CD8^+$ (bottom).

rounded rete ridges, known as a psoriasiform lichenoid pattern is particularly common. A pattern resembling interface dermatitis is present in more than half of the biopsies.[13] Early patches of MF usually lack eosinophils or plasma cells.

The final diagnosis is based on a combination of specific histologic parameters without the necessity of confirmatory immunophenotyping in the vast majority of cases.[10,11] Both interobserver and intraobserver variability is generally high.[14]

In the thin plaque stage, the histological findings are more often fully diagnostic (Fig. 1B). There is a dense infiltrate with lymphocytes lining up in the basal layer, especially at the tips of the rete ridges with epidermotropism of single cells. The majority of cells are small, differentiated lymphocytes with round or only slightly cerebriform nuclei. Haloed cells may predominate in the epidermis. There may be mild acanthosis, hyperkeratosis, edema or fibrosis of the papillary dermis. There is proliferation of postcapillary venules with prominent endothelial cells, simulating histiocytic giant cells. The infiltrate may contain an admixture of eosinophils, plasma cells, macrophages, and dermal dendritic cells.[15,16]

The thick plaque stage (Fig. 1C) is typified by a dense, subepidermal, usually band-like infiltrate containing a high number of cells with cerebriform nuclei. Epidermotropism is more prominent with small intraepidermal clusters (two to three cells) of lymphocytes. Typical Pautrier microabscesses are seen only in approximately 10% of cases. Subcorneal bullous formation may result from confluence of Pautrier microabscesses.[17]

With progression from plaque stage to tumor stage (Fig. 1D), the dermal infiltrates become more diffuse, and epidermotropism may disappear. The proportions of tumor cells increase both in number and size, and may include cells with small, medium-sized and large cerebriform nuclei, and blast cells with prominent nuclei and intermediate forms. There is a concomitant decrease in the numbers of reactive T cells and dendritic cells. Eosinophils and plasma cells usually are present.

Immunophenotype

The immunophenotypical prototype of MF is a $CD2^+$, $CD3^+$, $CD4^+$, $CD5^+$, $CD45RO^+$, $CD8^-$, $TCRbeta^+$, and $CD30^-$ phenotype (Fig. 1E) $CD4^{--}$. A $CD8^+$ phenotype has been described (Fig. 1F), which otherwise seems to be similar to MF. During progression of the disease loss of CD7, CD2 and CD5 may be seen especially in the epidermotropic cerebriform cells. When large blast stage occur in tumors (large-cell transformation), $CD4^+$ epidermotropic cells can express a cytotoxic phenotype (TIA-1 and granzyme B) and CD30. Rare cases of $CD56^+$ MF have also been observed.[18]

Molecular findings and genetics

Monoclonal rearrangement of T-cell receptor gamma genes is a common finding in plaque and tumor stage of MF but is found in only half of the cases of early MF.

There are only very few data on chromosome aberrations in primary CTCL. Molecular cytogenetic analysis of CTCL using comparative genomic hybridization (CGH) analysis has identified common genetic alterations in SS and MF.[19] The most frequent losses involve chromosomes 1p, 17p, 10q/10 and 19. Commonly detected chromosomal gains involve 4/4q, 18 and 17q/17. A similar pattern of chromosomal instability is seen in both MF and SS.[19] Numerical aberrations of chromosomes 6, 13, 15, and 17, marker chromosomes, and structural aberrations of chromosomes 3, 9, and 13 were increased in MF compared with healthy controls.[20]

Detailed molecular expression analysis of cutaneous T-cell lymphoma is not available. Some oncogenic alterations have been demonstrated, such as functional inactivation of the Fas receptor[21] constitutive activity of STAT3,[22] or the inactivation of the $p16^{INK4a}$ gene via deletion or promoter hypermethylation.[23,24]

On the other hand, inactivation of several tumor suppressor genes in CTCL, such as SHP-1,[25] p15, p16,[26] and hMLH1[27] has been reported. Protein expression and phosphorylation assays revealed that lack of SHP-1 expression, an important negative regulator involved in signaling through receptors for cytokine/growth factors such as c-*kit* ligand, interleukin (IL)-3, IL-2, IL-4, and IL-13 and others, is frequent in malignant T cells and results from methylation of the SHP-1 gene promoter. The persistence of signals generated by IL-2R and possibly other receptor complexes may be important in the pathogenesis of T-cell lymphomas.[25] Whittaker and colleagues showed aberrant p15 protein expression in 85% of patients analyzed with p15 gene abnormalities and abnormal p16 expression in 59% with p16 gene abnormalities. These abnormalities were not dependent on cutaneous stage of disease, leading to the suggestion that abnormalities of the p15 and p16 genes may be common in both early and advanced stages of MF and SS and that these genes may be inactivated by allelic loss and aberrant promoter methylation.[26] Microsatellite instability (MSI) was found to be more prevalent in tumor stage MF than early-stage disease and was associated with an older age of onset of MF.[27] In more than half of the patients with MSI, abnormal hMLH1 protein expression could be detected, and

it has been argued that the development of a mutator phenotype may contribute to disease progression in MF. Recently, a genome-wide scale differential methylation hybridization analysis, comparing aggressive CTCL entities such as transformed MF and $CD30^-$ large T-cell lymphoma with indolent entities ($CD30^+$ large T-cell lymphoma) revealed a relative hypermethylated state of putative tumor suppressor genes such asbcl7a, PTPRG, and thrombospondin.[28] The hypermethylated state of several tumor suppressor genes involved in DNA repair, cell cycle, or apoptosis, lead to inactivation of these genes, thus promoting leukemogenesis of CTCL. Whether these events are causative or an epiphenomenon remains to be elucidated. Tumor suppressor gene hypermethylation may render these tumors amenable to therapeutic interventions with demethylation agents.

A study employing microsatellite analysis of microdissected tumor tissue suggested that CTCL may evolve by multilineage progression and that tumor subclones in MF can be detected in early disease stages.[29]

Variants and subtypes

Apart from the classical form of MF, there are several variants and subtypes of this disease including folliculotropic MF, pagetoid reticulosis and granulomatous slack skin. Apart from those listed in the WHO/EORTC classification, there are bullous, granulomatous, hypo- or hyperpigmented, hyperkeratotic and other forms of MF.[30,31]

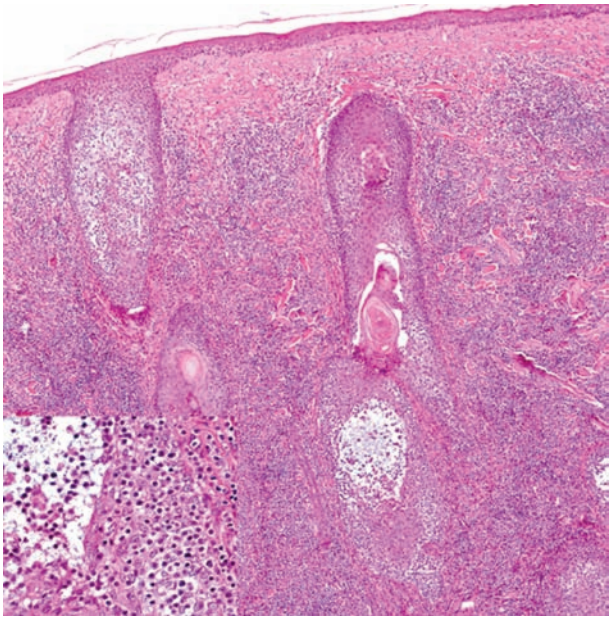

Fig. 2. Follicular mycosis fungoides (MF): deep dense lymphocytic infiltrate with folliculotropism but low epidermotropism. Follicular epithelium shows mucinous degeneration forming mucin lakes. Inset: detailed view of atypical lymphocytes infiltrating the follicular epithelium.

Folliculotropic MF (pilotropic MF, folliculocentric MF) with or without follicular mucinosis shows a predilection for hair follicles. Clinically, the disease manifests itself as erythematous patches or plaques with follicular hyperkeratosis producing comedo-like plugs and often hair loss. The face and upper trunk are the sites of predilection. Pseudotumorous forms dominated by follicular epithelial hyperplasia rather than lymphocytic proliferation have been reported.[32]

Histologically, there is a dense lymphocytic infiltrate of small to medium-sized cells with irregular nuclei, surrounding and infiltrating the hair follicles and sparing interfollicular areas (Fig. 2). Often, nuclear atypia of lymphocytes is not prominent.[33] The follicles may show cystic dilatation, cornified plugging and in some cases mucin deposition. Since some patients experience an aggressive clinical course with large-cell transformation and lymph node involvement, folliculotropic MF carries a worse prognosis than classic MF.[34–36] Changes in intercellular adhesion receptors may account for the phenomenon of folliculotropism in follicular MF.

Pagetoid reticulosis (PR) is a low-grade malignant variant of MF with characteristic histologic features, but various phenotypes. Originally two forms of PR were described, namely disseminated by Ketron and Goodman[37] and unilesional PR in 1931 by Woringer and Kolopp.[38] The term 'pagetoid reticulosis' was proposed by Braun-Falco and colleagues because of the clinical and the histological appearance.[39] Clinically, the differential diagnosis of the unilesional form includes solitary lesions of psoriasis, Bowen disease, extramammary Paget disease, or circumscribed forms of chronic dermatitis. Histologically, the acanthotic epidermis shows sponge-like disaggregation by medium-to-large-sized atypical lymphoid cells with vacuolated, abundant cytoplasm, singly or arranged in clusters[40] (Fig. 3A,B). Superficial spreading type of malignant melanoma and Paget disease may mimic PR but can readily be distinguished by cytomorphologic and immunophenotypic features (S-100; CEA; EMA).[41,42] Most cases of PR express a T-helper phenotype: $CD3^+$, $CD4^+$, $CD5^+$ and CD8–.[43] There are reports on $CD8^+$ cases[44,45] or PR expressing a gamma/delta phenotype[46] which should be classified among the gamma/delta T-CL. The pronounced epidermotropism of neoplastic cells in PR may be due to their strong expression of receptors (CLA and alpha E beta 7), seen also in non-neoplastic conditions, interacting with endothelial cells and keratinocytes, respectively.[47]

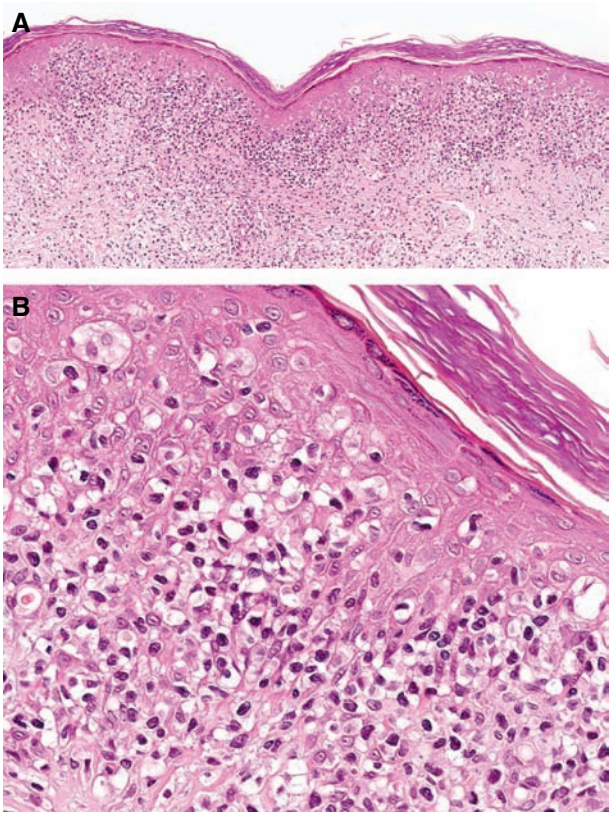

Fig. 3. A) Pagetoid reticulosis: mostly superficial lymphocytic infiltrate showing prominent epidermotropism with spongiform disaggregation of the epidermis. B) Pagetoid reticulosis: prominent epidermotropism of lymphocytes with nuclear atypia and clear cytoplasm (halo cells).

Granulomatous slack skin (GSS)

Granulomatous slack skin (GSS) is a rare form of CTCL, nosologically related to MF and is therefore referred to as subtype of MF in the WHO/EORTC classification, clinically characterized by the development of bulky skin lesions in the major skin folds. The differentiation between variant and subtype of an entity is somehow arbitrary but is helpful in pointing to minor (variants) and major (subtype) differences from the prototype CTCL (MF). This nomenclature is also used for extracutaneous tumors of the hematopoietic and lymphoid tissues.[6]

Synonyms in other classifications

WHO/EORTC classification (2005): subtype of mycosis fungoides
WHO classification (2001): not listed
REAL classification (1997): not listed
EORTC classification (1997): granulomatous slack skin

Histology

Early lesions of GSS display a band-like infiltrate of small lymphocytes without significant nuclear atypia.[48] More advanced lesions show a dense lymphocytic infiltrate throughout the entire dermis, but unlike tumors of MF, the lymphocytes are usually small. The diagnostic hallmark is numerous multinucleated histiocytic giant cells, which are scattered throughout the background of the dense lymphocytic infiltrate. These giant cells contain 20–30 nuclei mostly located at the periphery of the cytoplasm (Fig. 4), Elastophagocytosis and emperipolesis, i.e. phagocytosis of lymphoid cells by multinucleated giant cells, are present. Elastic stains demonstrate the loss of elastic fibers at the sites of the infiltrates in all dermal layers. Ultrastructurally, the lymphocytes show hyperchromatic cerebriform nuclei similar to those seen in MF and SS.[49]

Immunophenotype

The lymphoid tumor cells display a T-helper phenotype with the expression of CD4, CD45RO. There may be loss of other T-cell markers such as CD3, CD5, or CD7. In rare cases, the tumor cells express CD30.[50] The giant cells are of histiocytic origin and thus are positive for histiocytic markers such as CD68 and Mac387.

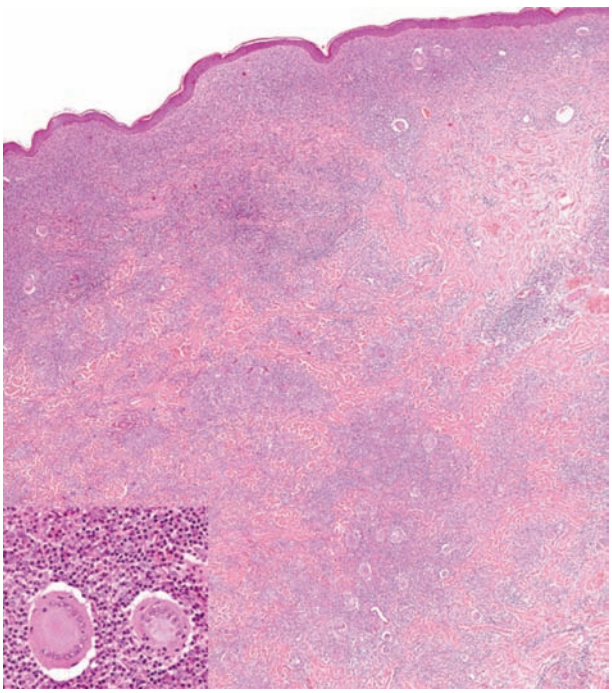

Fig. 4. Granulomatous slack skin: dense superficial and deep lymphocytic infiltrate with numerous scattered large, histiocytic multinucleated giant cells (detail in the inset).

Molecular findings and genetics

Clonal rearrangement of TCR genes can be found in most cases and is a useful diagnostic tool in early stages of the disease.[51] Trisomy 8 has been reported in two cases.[52–54]

No molecular expression analysis has been reported, probably because of the rarity of the disease.

Sézary syndrome (SS)

This leukemic form of CTCL is defined by erythroderma, lymphadenopathy, and presence of neoplastic T-cells (Sézary cells) in skin, lymph nodes, and peripheral blood with an absolute Sézary cell count of at least 1000 cells/mm^3. Clinically edema, hyperkeratosis of palms and soles, and therapy-resistant pruritus are typically present. Recently, the following criteria for the diagnosis of SS were recommended by the International Society for Cutaneous Lymphoma (ISCL): an absolute Sézary cell count of at least 1000 cells/mm^3; demonstration of immunophenotypical abnormalities (expanded CD4$^+$ T-cell population resulting in a CD4/CD8 ratio more than 10 and loss of any or all of the T-cell antigens CD2, CD3, CD4, and CD5, or both); or the demonstration of a T-cell clone in the peripheral blood by molecular or cytogenetic studies.[55]

Synonyms in other classifications

WHO/EORTC classification (2005): Sézary syndrome
WHO classification (2001): Sézary syndrome
REAL classification (1997): Sézary syndrome
EORTC classification (1997): Sézary syndrome

Histology

The histological spectrum of SS is similar to that of MF although there are minor differences.[56,57] Although Pautrier microabscesses and acanthosis are more frequently present in SS than in MF, however, recent studies suggest that histological features do not reliably allow differentiation between the two disorders.[56,58]

The most prevalent finding in skin biopsies from SS patients is a subepidermal perivascular or band-like monotonous infiltrate composed of predominantly small lymphocytes with or without nuclear atypia (Fig. 5A).[15,59] A few eosinophils and plasma cells may be admixed. The epidermis often shows psoriasiform acanthosis. Epidermotropism and lining up of lymphocytes with cerebriform nuclei (MF-like pattern) is found in approximately 20–40%, half of which exhibit Pautrier microabscesses[59,60] which are a specific, but not a regular finding in epidermotropic CTCL such as MF and SS[57] (Fig. 5B). Edema is often present in initial stages of epidermotropic CTCL but may be replaced over time by fibrosis of papillary dermis. Occasionally, granulomatous features can be seen in SS lesions.[59,61] Both intraobserver and interobserver variability is high in the diagnosis of SS.[62] Non-specific findings are present in one-third of the biopsies.[60]

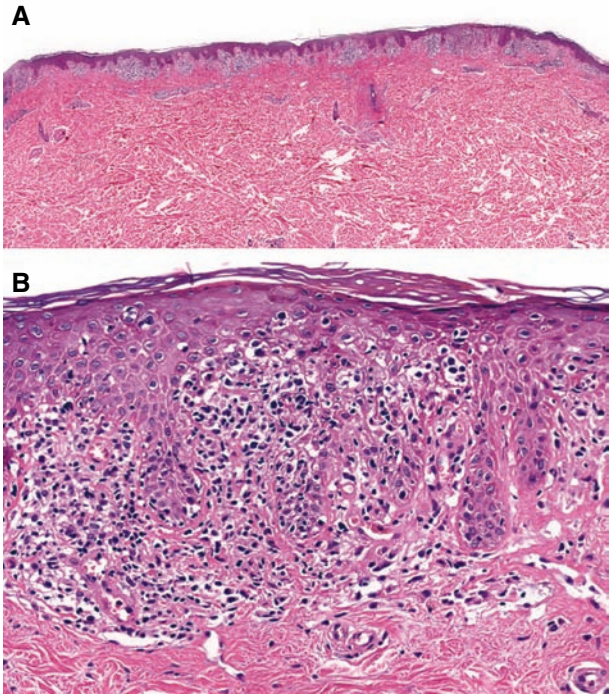

Fig. 5. A) Sézary syndrome: slight acanthosis and superficial, perivascular lymphocytic infiltrate with epidermotropism. B) Sézary syndrome: detail epidermotropism of lymphocytes with formation of Pautrier's microabscesses.

Immunophenotype

Sézary cells are mature helper T cells with a memory cell phenotype, showing the following immunoprofile: CD2, CD3, CD4, CD5, CD45 RO, and CD30$^-$.[63] The majority of SS cells are also CLA^{+64} and CD7$^-$.[65] However, further studies have shown that the neoplastic cell population is present in both the CD7$^+$ and CD7$^-$ subset in the same patient.[63] More recently, Bernengo et al.[66] have demonstrated that CD4$^+$ SS cells typically loose CD26 and that a diagnosis of SS or MF with hematological involvement can be made if the CD26 subset exceeds 30% of the CD4$^+$ cells.[65] In about two-third of patients with SS, complete loss of T-cell antigens such as CD2, CD3, CD4, or CD5 may be found.[66]

Molecular findings and genetics

Using multiplex-fluorescence *in situ* hybridization (M-FISH) and CGH, recurrent unbalanced translocations associated with deletions can be detected in samples from SS patients. Characteristic cytogenetic

abnormalities in SS particularly involve 1p, 10q, 14q, and 15q.[67] The dominant chromosome changes in SS appear to be numerical losses rather than structural aberrations, and as of yet, no reciprocal balanced translocations with a leukemogenic candidate fusion gene such as *RA-PML* in promyelocytic leukemia have been detected. Chromosome losses have been associated with clonal evolution during disease progression through non-disjunction of chromosomes. The underlying causative chromosomal instability in SS cells remains yet to be elucidated in cell-cycle checkpoint studies.

An alternative approach to clarify important molecular events in cutaneous lymphoma has been taken on by SEREX-based identification of a tumor-specific antigen.[68] A heterogeneous expression pattern of cancer/testis antigens has been demonstrated in SS, including Gage, MAGE-1, MAGE-3, MAGE-C1, NY-ESO-1, and TS85.[69] Recently, two differentiation antigens p140 and SCS have been reported in circulating SS cells, and p140 was also found in skin-infiltrating cells of patients with SS.[70] No differences in expression of cellular interaction molecules, such as ICAM-1, LFA-1, CD40, and CD40 ligand, exist between MF and SS.[58]

The signal transducers and activators of transcription (STAT) family members play an important role in regulating T-cell activation.[71] Dysregulated expression of $STAT5_t$, a naturally occurring COOH-terminal truncated isoform of STAT5, in malignant T cells in SS syndrome can suppress STAT5-dependent gene expression, which may, in turn, contribute to the cellular transformation.[72]

More recently, oligonucleotide array analysis has allowed gene expression comparison between SS cells and $CD4^+$ T cells isolated from the blood of patients with erythroderma secondary to atopic or chronic dermatitis and of healthy volunteers. For the analysis, the authors included SS patients with a high percentage of $CD4^+$ SS cells in the peripheral blood mononuclear cells. The SS samples displayed a relatively homogeneous gene-expression pattern and could be distinguished from benign $CD4^+$ T cells using an unsupervised hierarchical clustering analysis algorithm. Two genes (Twist and Ephrin A4) were consistently upregulated, whereas transcripts were nearly undetectable in any of the control samples in microarray experiments and consecutive real-time quantitative PCR. The Twist gene encodes a basic helix-loop-helix family transcription factor involved in mesodermal differentiation and is normally not expressed in lymphoid cells.[73,74] An oncogenic property of Twist has been proposed via prevention of c-myc-induced apoptosis by antagonizing the p53 pathway.[75] Ephrin A4 (EphA4) belongs to the Eph receptor subfamily of transmembrane protein–tyrosine kinases that are preferentially expressed in neurons but has also been detected in human T cells. Its involvement in tumorigenesis is attractive, as it has been shown that EphA4 can activate the JAK/STAT pathway.[76,77] EphA4 expression in CTCL has not been reported at the protein level. If indeed activation of EphA4 can be pinpointed as an early or crucial event in transformation of T cells, it may be an attractive target for antitumor therapy, analogous to the success story of inhibition of BCR-ABL by imatinib in chronic myelogenous leukemia patients.

Consistent with earlier reports, high expression of JunB, versican, TRAIL, T-plastin, Kir3DL2, integrin β_1, as well as low expression of STAT4, TGF-β receptor II, Fas, and CD26 have been found in SS T cells. Contradictory to previous reports, increased rather than decreased levels of TIA-1 and SHP-1 tumor suppressor transcripts were recently described.[78] Kari and colleagues[79] performed filter array analysis on partly purified SS cells, and compared their expression pattern to *in vitro* Th1- and Th2-skewed PBMCs. The array data were validated by real-time qPCR. One of the main objectives was to develop biomarkers for identification of clinically difficult-to-detect patients with low tumor burden. This study suggested that the loss of expression of Th1-skewing STAT4, together with increased expression of RhoB and other genes, can be used in penalized discriminant analysis (PDA[80]) to separate patients with SS cell counts as low as 5% from control patients with inflammatory diseases or from Th2-skewed blood samples. In addition, short-term survivors of SS syndrome, independent of their tumor burden, have a detectably different gene expression pattern from patients classified as long-term survivors. One explanation could be that the malignant cells impose, via their direct or indirect cytokine release, an expression pattern on other PBMCs that may be detected as a CTCL signature.

The two published gene-expression analysis studies on SS cells address different questions, rely on different sampling of patient material, and use different data analysis methods, perhaps explaining the study discrepancies. For a more accurate study of expression analysis of tumor cells in SS syndrome, a thorough clone purification by fluorescence-activated cell sorting of the Vβ TCR domain may prove to be advantageous.

$CD30^+$ T-cell lymphoproliferative disorders of the skin

$CD30^+$ T-cell LPD of the skin ($CD30^+$ LPD) comprise a clinical and morphologic spectrum of diseases including lymphomatoid papulosis (LyP), primary cutaneous anaplastic large-cell lymphoma

(ALCL), as well as so-called borderline cases.[81–83] The hallmark of the tumor cells is the expression of CD30, a cytokine receptor belonging to the tumor necrosis factor receptor (TNFR) superfamily. Although they share CD30 expression as a common immunophenotypic feature, the diseases within the group of $CD30^+$ LPD differ in their clinical and histological presentations.[84,85] The final diagnosis has to include careful correlation of histologic findings with clinical manifestations of the disease when evaluating infiltrates with $CD30^+$ tumor cells.[86]

Lymphomatoid papulosis

Lymphomatoid papulosis (LyP), described in 1968 by Macaulay, is a chronic recurrent, self-healing papulo-nodular skin eruption with histologic features of a malignant lymphoma.[87]

Synonyms in other classifications

WHO/EORTC classification (2005): CD30 lymphoproliferative disorders of the skin – lymphomatoid papulosis
WHO classification (2001): CD30 lymphoproliferative disorders of the skin – lymphomatoid papulosis
REAL classification (1997): not listed
EORTC classification (1997): lymphomatoid papulosis

Histology

The histological features of LyP are variable and depend on the stage of the lesions and disease. Three histologic patterns have been differentiated (Table 2).[88,89] In type A (Fig. 6A), tumor cells are large atypical cells, resembling Reed-Sternberg-like cells (Fig. 6B). In type B, a band-like infiltrate of small cerebriform cells is found. The type C lesions exhibit large atypical lymphoid cells growing in cohesive sheets with only a few intermingled reactive inflammatory cells (Fig. 6C). Epidermotropism can be present. In addition, in type A lesions, there are numerous inflammatory cells such as neutrophils, eosinophils, and histiocytes as well as few plasma cells and a prominent edema in the upper dermis. Variants of lymphomatoid papulosis include cases with a perifollicular distribution and those with lymphocytic vasculitis or dermal mucin deposits.[88] There may be various histologic types in individual patients at the same time, depending also on the stage and age of the lesion.[90]

Differentiation between LyP and other $CD30^+$ LPD must be based on correlation of clinical presentation and histologic findings.

Immunophenotype

The tumor cells in LyP express the marker profile of mature T cells [$CD3^+$, $CD4^+$, $CD8^-$, $CD30^+$, and $CD56^+$ (10%)] (Fig. 6D) and of activated T cells [HLA-DR and CD25 (interleukin 2-receptor)], thus representing a proliferation of activated T-helper cells.[91–95] Usually one or more T-cell antigens such as CD2 and CD5 are expressed, whereas CD7 expression is often absent. CD15, which is a characteristic marker for Reed-Sternberg cells in Hodgkin lymphoma, is not expressed by tumor cells in LyP. In contrast to tumor cells expressing CD30 as a hallmark of LyP type A and type C, the small tumor cells with cerebriform nuclei in LyP type B are usually negative for CD30. Recent studies indicate that almost all tumor cells in LyP and ALCL express cytotoxic molecules such as TIA-1 and granzyme B.[96] The presence of large $CD30^+$ T cells is not diagnostic *per se* for LyP, as there is an enlarging number of benign reactive conditions in which $CD30^+$ cells can be found.[97]

Molecular findings and genetics

The findings of translocation studies for t(2;5) are controversial, showing translocation and the t(2;5)-associated p80 NPM/ALK fusion protein in some $CD30^+$ cutaneous lymphoma and LyP[98,99] whereas it is absent in most cases.[100] Furthermore, conflicting data on the detection of clonality among the large $CD30^+$ tumor cells and small lymphocytes have been reported.[101,102] On the other hand, in cases in which LyP is associated with MF, both diseases have been shown to harbor the same T-cell clone, indicating that both diseases are different clinical manifestations of the same T-cell proliferation.[103]

Primary cutaneous anaplastic large-cell lymphoma

Primary cutaneous and primary nodal $CD30^+$ ALCL are distinct clinical entities which share histologic features and display a certain overlap in immunophenotype, but differ in age of onset,

Table 2. Histologic types of lymphomatoid papulosis (Lyp)[89]

Histologic type	Morphologic criteria
LyP type A	Scattered $CD30^+$ blast cells in an extensive inflammatory infiltrate
LyP type B	Mycosis fungoides-like features with atypical small $CD30^-$ T cells with cerebriform nuclei and epidermotropism
LyP type C	Large clusters of $CD30^+$ cells with few inflammatory cells, histologically suggesting ALCL

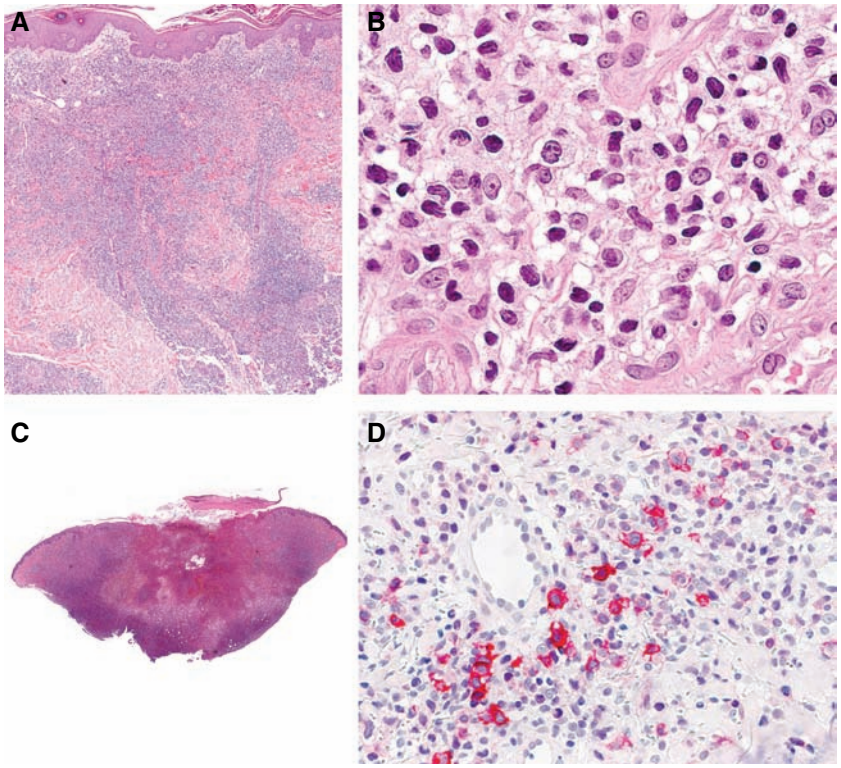

Fig. 6. A) Lymphomatoid papulosis: dense superficial and deep wedge-shaped infiltrate, slight acanthosis, and parakeratosis of the overlying epidermis. B) Lymphomatoid papulosis: Medium-to-large-sized pleomorphic or anaplastic tumor cells. C) Lymphomatoid papulosis: dense superficial and deep lymphocytic infiltrate with central necrosis and ulceration. D) Lymphomatoid papulosis: tumor cells show CD30 positivity.

genetic features, etiology, and prognosis.[104–106] Clinically, cutaneous ALCL presents as a single or multiple grouped nodules or tumors, confined to one extremity or body area.

Synonyms in other classifications

WHO/EORTC classification (2005): primary cutaneous anaplastic large-cell lymphoma
WHO classification (2001): primary cutaneous anaplastic large-cell lymphoma
REAL classification (1997): anaplastic large-cell lymphoma, $CD30^+$
EORTC classification (1997): primary cutaneous large-cell T-cell lymphoma, $CD30^+$

Histology

There is a dense nodular infiltrate of atypical lymphoid cells with pleomorphic, anaplastic, or immunoblastic cytomorphology, extending through all levels of the dermis into the subcutis (Fig. 7A). Epidermotropism is an inconsistent feature. The morphologic hallmark are large, bizarre cells with irregularly shaped nuclei and one or multiple nucleoli. They may be multinucleated, and often have abundant, pale, or eosinophilic cytoplasm (Fig. 7B). Tumor cells usually grow in dense cohesive sheets, reminiscent of nodular malignant melanoma or undifferentiated carcinoma. Mitoses are frequent. Clusters of small reactive lymphocytes are found within and around the tumor. Eosinophils, plasma cells, and accessory dendritic cells usually are not prominent in ALCL. Neutrophil-rich or pyogenic $CD30^+$ ALCL features small aggregations or scattered $CD30^+$ medium-to-large pleomorphic lymphoid cells within an extensive infiltrate of neutrophils.[107,108] Recently, keratoacanthoma-like epidermal hyperplasia overlying the lymphoid infiltrate was reported.[109]

Immunophenotype

ALCL is defined by CD30 expression of at least 75% of the large pleomorphic, anaplastic, or immunoblastic lymphoid cells (Fig. 7C). Primary cutaneous $CD30^+$ ALCL have an activated T-cell phenotype with expression of T-cell-associated antigens CD2, CD3, CD4, and CD45RO and activation markers such as CD25 (IL-2R), CD30, CD71, and HLA-DR. Variable loss of T-cell antigens (CD2, CD3, and CD5) can be found.[110] Expression of T-cell markers on tumor cells is usually weaker than on reactive lymphocytes.[110] In contrast to nodal ALCL, primary cutaneous forms do not express EMA but may express the cutaneous lymphocyte antigen (CLA and HECA-452) and homeobox gene HOXC5.[111] Primary cutaneous ALCL is negative for the anaplastic lymphoma-related tyrosine kinase (ALK) in the vast majority of cases.

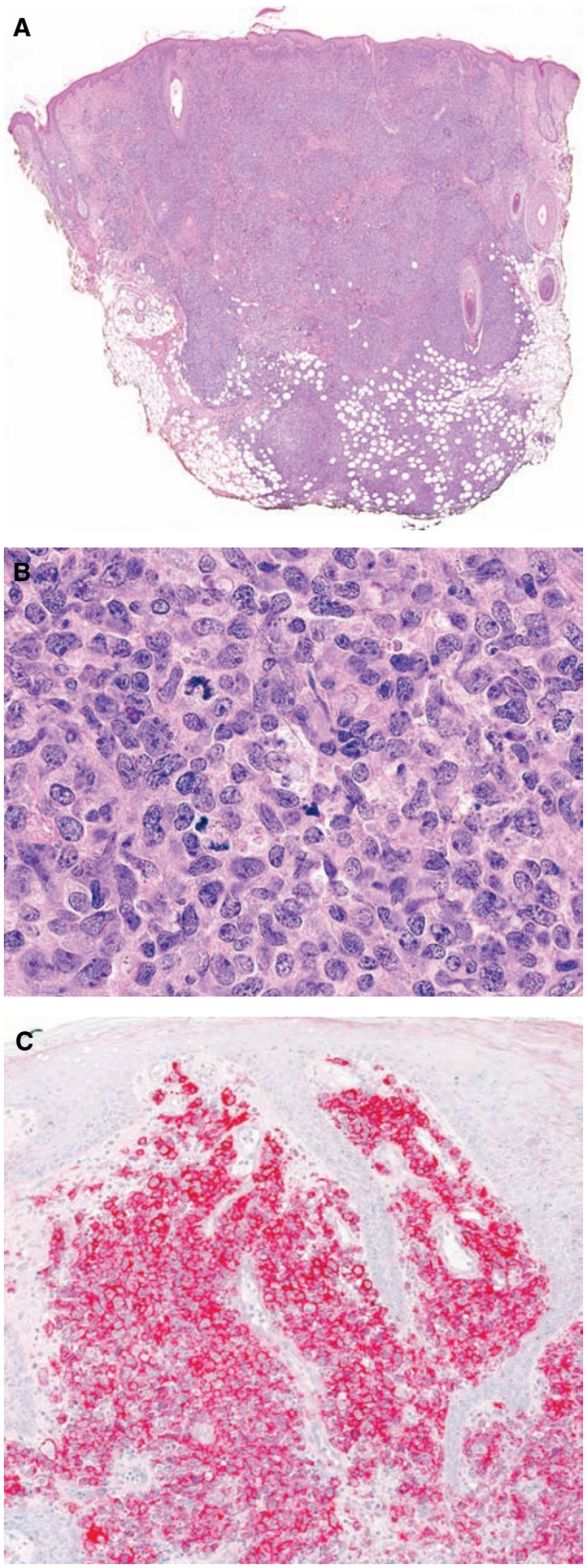

Fig. 7. A) Primary cutaneous ALCL: deep reaching circumscribed infiltrate of pale lymphoid cells. B) Primary cutaneous ALCL: dense infiltrate of large lymphoid cells with broad cytoplasm and pleomorphic or anaplastic nuclei with coarse chromatin. Mitotic activity is high. C) Primary cutaneous ALCL: characteristic CD30 positivity.

Molecular findings and genetics

Over 90% of cases of primary cutaneous ALCL display clonal rearrangement of TCR genes by Southern blot and PCR.[112] A high percentage of nodal $CD30^+$ ALCLs have a t(2;5)(p23;q35) translocation resulting in expression of t(2;5)-associated p80 NPM/ALK fusion protein. This translocation is never or extremely rarely found in primary cutaneous $CD30^+$ lymphomas. This is of particular importance because lack of ALK expression in cutaneous lymphomas is not a prognostic factor, whereas ALK^- nodal lymphomas show a significantly worse prognosis compared to their ALK^+ counterparts.[113] Systemic ALCL may present with cutaneous disease, and the identification of ALK expression is helpful in this distinction. In primary cutaneous ALK^--ALCL, disease progression is not dependent on p53 mutation or conversion to ALK positivity.[114]

A recent study on gene expression pattern comparing ALK^+ and ALK^- tumor cells of primary systemic ALCL showed significant discriminator cDNAs allowing a correct grouping of all ALK^+ and ALK^- tumors. However, a clear picture of the dominant signal-transduction pathway activated by NPM-ALK failed to emerge from this microarray data.[115]

Subcutaneous panniculitis-like T-cell lymphoma

Subcutaneous panniculitis-like T-cell lymphoma (SPTCL) is a lymphoproliferative disease originating and presenting primarily in the subcutaneous fat tissue, simulating panniculitis. Only SPTCLs expressing an α/β phenotype are referred as SPTCL *sui generis* in the WHO/EORTC classification, whereas cases with a γ/δ phenotype are included in the group of peripheral T-cell lymphomas, not otherwise specified (NOS).

Synonyms in other classifications

WHO/EORTC classification (2005): subcutaneous panniculitis-like T-cell lymphoma
WHO classification (2001): subcutaneous panniculitis-like T-cell lymphoma
REAL classification (1997): subcutaneous panniculitis-like T-cell lymphoma
EORTC classification (1997): subcutaneous panniculitis-like T-cell lymphoma

Histology

The histopathologic hallmark of this type of CTCL is the subcutaneous localization and growth pattern of usually non-epidermotropic focal infiltrates, which involve predominantly the lobules of the subcutaneous fat and simulate lobular panniculitis

(Fig. 8).[116,117] Karyorrhexis and fat necrosis are prominent features. The neoplastic lymphocytes usually have hyperchromatic nuclei. Their sizes range from small cells with round nuclei and inconspicuous nucleoli to larger transformed cells with hyperchromatic nuclei. Rimming of adipocytes by tumor cells is a common, but not specific, finding for SPTCL (Fig. 8). Many vacuolated and foamy histiocytes are found especially in areas of infiltration and destruction, and erythrophagocytosis can be present. Since the lymphoproliferative process is focal, broad and deep biopsies are required to establish the diagnosis. Cutaneous γδ T-cell lymphomas can have a panniculitis-like component, but commonly show both dermal and epidermal involvement in addition to subcutaneous disease.[118–121] Plasma cells and reactive lymphoid follicles are generally absent, in contrast to lupus profundus, and other forms of lobular panniculitis.

In some cases of SPTCL, the infiltrates in initial phases may appear deceptively reactive, and the differential diagnosis may be difficult.[122,123] As the disease evolves, the dermis may become involved by tumoral infiltrates.[124] Biopsies may demonstrate either a non-specific panniculitis or lipomembranous panniculitis with calcified lipomembranes. Therefore when SPTL is suspected, continued follow-up with repeated biopsies is important.[125]

Immunophenotype

Because the phenotype of tumor cells has been linked to aggressiveness of the disease, immunophenotyping has both therapeutic and prognostic implications.

Tumor cells are derived from αβ T cells with a cytotoxic profile. They express T-cell-associated antigens $CD2^+$, $CD3^+$, $CD5^+$, $CD4^-$, $CD8^+$, $CD43^+$, and cytotoxic proteins such as TIA-1, granzyme B, and perforin.[117] A TCR α/β ($\beta F1^+$) phenotype is found. Clonal rearrangement of TCR genes is present in the majority of the cases. Rarely, $CD30^+$ forms of SPTCL have been described.[126,127]

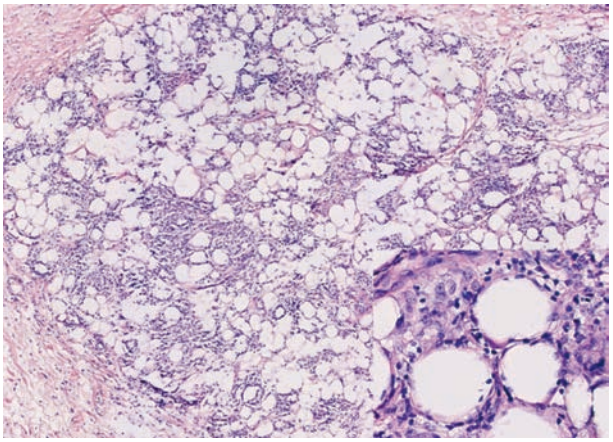

Fig. 8. Subcutaneous panniculitis-like T-cell lymphoma: Mostly lobular lymphoid infiltrate resembling lobular panniculitis; inset shows rimming of lymphocytes around adipocytes.

Molecular findings and genetics

The neoplastic cells show rearrangement of T-cell receptor genes. In a series of six patients from the UK those derived from γ/δ T cells carried a poor prognosis and were $CD56^+$, while a more indolent group was derived from αβ T cells.[120] Takeshita and colleagues[128] showed in 22 Japanese patients that the 11 cases with $CD56^-$ SPTCL cells had characteristics of $CD3\epsilon^-$, $CD8^-$, $TcR\beta F1^-$, $TIA\text{-}1^-$, and granzyme B^+ T cells and were negative for apoptosis-promoting proteins CD95 (Fas), Bax, CPP32 (caspase 3), and p53. On the other hand, the 11 $CD56^+$ cases presented with tumor cells positive for CD3ϵ, TIA-1, granzyme B, CD95, CD95L (FasL), Bax, and CPP32.

Some cases of SPTCL, particularly in Asians, were reported to be associated with EBV.[129] Most cases of SPTCL in Western countries are EBV^-.[117,118,122] EBV and CD56 positivity can result in confusion with nasal type NK lymphoma, which often involves the subcutis.

Primary cutaneous peripheral T-cell lymphoma, unspecified (PTL, NOS)

This category of peripheral T-cell lymphomas encompasses per definition all T-cell neoplasms that do not fit into any of the better defined subtypes of T-cell lymphoma/leukemia. As such it constitutes a heterogeneous group of diseases, representing less than 10% of all CTCL.[130] They are $CD30^-$ and show an aggressive behavior in most, but not all cases.

The following disorders have been included as provisional entities in the group of PTL:

1. Cutaneous gamma/delta T-cell lymphoma
2. Primary cutaneous aggressive epidermotropic $CD8^+$ cytotoxic T-cell lymphoma
3. Primary cutaneous $CD4^+$ small/medium-sized pleomorphic T-cell lymphoma

Cutaneous gamma/delta T-cell lymphoma

Cutaneous γ/δ T-cell lymphoma (CGDTCL) is a clonal proliferation of mature, activated γ/δ T cells expressing a cytotoxic phenotype. This group includes cases of SPTCL with a γ/δ phenotype. In the 2001 WHO classification, these were grouped together with SPTCL of α/β origin.[131] Whether cutaneous and mucosal γ/δ TCL are all part of the same disease spectrum is unclear.[132–134]

Histology

Three major histologic patterns can be seen: epidermotropic, dermal, and subcutaneous. Usually more than one histologic pattern is present in the same patient either in different specimens or within a single biopsy. Epidermal infiltration may occur, ranging from mild epidermotropism to marked pagetoid reticulosis-like infiltrates.[46,135,136] Subcutaneous nodules may be panniculitis-like or more solid in appearance and may show rimming of fat cells similar to SPTCL of α/β origin.[137] Dermal and epidermal involvement often coexists with subcutaneous disease, in contrast to SPTCL of α/β origin, which is mainly or exclusively subcutaneous in distribution.[117,120,137] The neoplastic cells are generally medium to large in size with coarsely clumped chromatin and irregular nuclei. Apoptosis and necrosis are common, often with vascular invasion.[137]

Immunophenotype

The cells are $CD3^+$, $CD2^+$, $CD43^+$, $CD45RO^+$, $CD15^-$, $CD30^-$, $CD20^-$, $CD25^-$, and $CD7^{+/-}$, but usually negative for CD5.[132] Most CGDTCLs lack both CD4 and CD8 but some are $CD8^+$[121] and may express natural killer cell-associated antigens such as CD56.[137] The cells are positive for TCR γ/δ in frozen sections but lack βF1, a formalin-resistent epitope of the α/β T-cell receptor. As most laboratories only perform immunohistochemical studies on formalin-fixed paraffin embedded tissues, a lack of staining for β-F1 in an infiltrate that has a T-cell phenotype is the best way to infer the diagnosis of CGDTCL at present. The neoplastic cells are positive for TIA-1 and the cytotoxic proteins granzyme B, granzyme M, and perforin.[118,137,138]

Molecular findings and genetics

The cells show clonal rearrangement of the TCR gamma gene. TCR beta may be rearranged or deleted, but is not expressed. Cases with predominant subcutaneous involvement express Vdelta2, but this has not been studied in other CGDTCL.[117,139] EBV is generally negative in primary CGDTCL.[134,140]

Primary cutaneous aggressive epidermotropic $CD8^+$ cytotoxic T-cell lymphoma

Clinically, this form of $CD8^+$ cutaneous lymphoma differs from the slowly progressive $CD8^+$ form similar to classic MF. It presents with erosive plaques rather than patches. It exhibits an unfavorable prognosis with rapid course.

Histology

There is a pagetoid pattern with prominent epidermotropism showing acanthosis, spongiosis, necrosis, and erosion (Fig. 9).[141] In some cases, angiocentric and angiodestructive features have been described.[142]

Immunophenotype

The tumor cells express CD3, CD8, CD7, CD45RA, CD45RO and beta F1 as well as TIA-1. The $CD2^-$, $CD7^+$ phenotype seems to be associated with a more aggressive course.[143] With disease progression, tumor cells may acquire CD7 or loose CD2.

Primary cutaneous $CD4^+$ small/medium-sized pleomorphic T-cell lymphoma

This is a non-cytotoxic CTCL characterized by a predominance of small to medium-sized $CD4^+$ pleomorphic T cells with clinical features not compatible with MF.

Histology

The diffuse or nodular lymphoid infiltrate is monomorphous, predominantly perivascular and periadnexal and shows a tendency to extend to the subcutaneous tissue. It consists of small-to-medium-sized pleomorphic lymphoid cells with irregular hyperchromatic nuclei and a pale scanty cytoplasm (Fig. 10).[144] A small proportion (<30%) of large pleomorphic cells may be present.[130] Mitoses are observed. Eosinophils and plasma cells and histiocytes may be admixed. Epidermotropism is absent

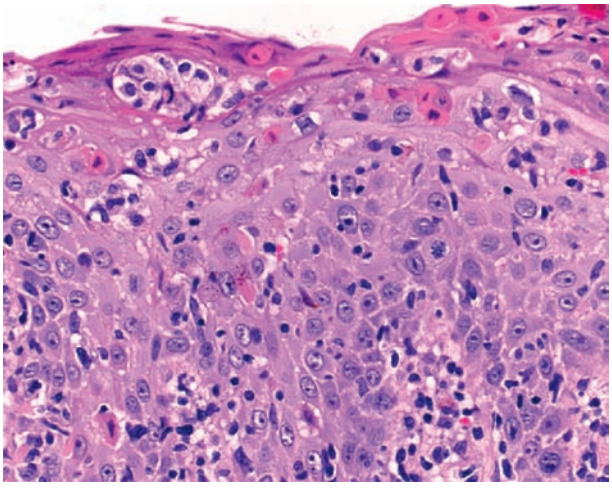

Fig. 9. Primary cutaneous aggressive epidermotropic $CD8^+$ cytotoxic T-cell lymphoma: pronounced epidermotropism and apoptotic keratinocytes.

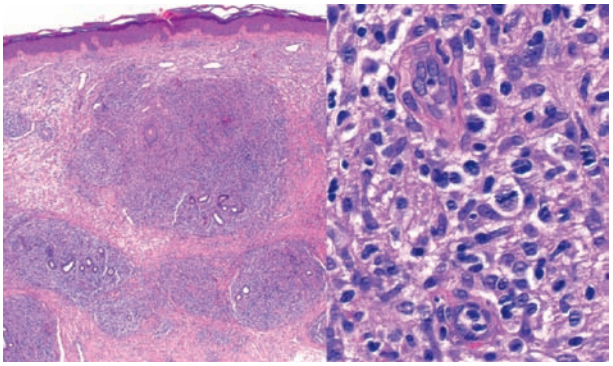

Fig. 10. Small-medium $CD4^+$ TCL: dermal nodular lymphoid infiltrate without epidermotropism (left) containing small to medium sized pleomorphic tumor cells (right).

in most cases, but granulomatous features are found in a subset of cases.[145]

Immunophenotype

These lymphomas have a $CD3^+$, $CD4^+$, $CD8^-$, and $CD30^-$ T-helper phenotype sometimes with loss of pan T-cell markers. Cytotoxic proteins are not expressed. $CD20^+$ B cells may be admixed.[146]

Molecular findings and genetics

Clonal rearrangement of TCR genes has been detected in almost all cases and may be useful in distinguishing SPTCL from reactive T-cell infiltrate (T-cell pseudolymphoma)[144] which may also present with a solitary plaque or nodule. No consistent cytogenetic abnormalities have yet been identified.

Cutaneous B-cell lymphomas

Cutaneous marginal zone B-cell lymphoma (MZL)

Synonyms in other classifications

WHO&/EORTC classification (2005): cutaneous marginal zone B-cell lymphoma
WHO classification (2001): extranodal marginal zone lymphoma of MALT type
REAL classification (1997): extranodal marginal zone B-cell lymphoma
EORTC classification (1997): primary cutaneous marginal zone B-cell lymphoma

Histology

The nodular or diffuse infiltrate is composed of small to medium-sized lymphocytes possessing slightly irregular nuclei with moderately dispersed chromatin and inconspicuous nucleoli and an abundant, pale cytoplasm (marginal zone cells)[147,148] (Fig. 11A). Some cells have a monocytoid appearance (reniform nuclei) or show prominent plasma cell differentiation[149] (Fig. 11B). The characteristic 'inverse pattern' may be seen on scanning magnification, typified by darker centers surrounded by brighter zones of pale-staining cells. Reactive germinal centers with distinct mantle zones are commonly found in early lesions but may become colonized by tumor cells as the disease progresses. The colonized follicles lack a distinct germinal center/mantle zone demarcation and have a more variable cellular composition, including marginal zone cells, centrocytes, and centroblasts. The cellular population in the interfollicular areas is represented by small to medium-sized, centrocyte-like, or monocytoid cells with slightly irregular nuclei, moderately dispersed chromatin, inconspicuous nucleoli, and a rim of pale cytoplasm.[147,148,150] Occasionally, the infiltrate is arranged around adnexal structures. Small lymphocytes can also surround and infiltrate eccrine coils, in a manner analogous to that found in the lymphoepithelial lesions of MALT lymphoma of the gastrointestinal tract[151] in some cases resulting in vertical columns of cells.[152]

Primary cutaneous marginal zone B-cell lymphoma includes cases previously designated as primary cutaneous immunocytoma[153] with high numbers of monotypic plasma cells and lymphoplasmacytoid cells showing intranuclear (Dutcher bodies) and intracytoplasmic PAS^+ globular inclusions, representing immunoglobulin deposits.

Immunophenotype

The neoplastic cells have the following immunophenotype: $CD19^+$, $CD20^+$, $CD22^+$, $CD79a^+$, $CD5^-$, $CD10^-$, $CD23^-$, bcl-6^-, bcl-2^+[154,155] (Fig. 11C–E). Monotypic expression of immunoglobulin light chains is seen in the majority of cases. It is best assessed in cases in which plasmacytoid cells are present in confluent aggregates rather than just occurring as single, scattered cells. CD21 staining often reveals regular and irregular networks of follicular dendritic cells (FDCs) corresponding to the sites of colonized follicles. In some cases large, expanded, diffuse FDC networks may be seen. Germinal center cells in the colonized and reactive follicles as well as in the expanded FDC networks are usually bcl-6^+ and bcl-2^-. $CD30^+$ blasts can often be found. There is a variable number of reactive $CD3^+$ T cells admixed to the neoplastic B cells (Fig. 11F).

Molecular findings and genetics

IgH genes are clonally rearranged in the majority (>70%) of cases.[156] The most common translocation in gastric MZL, the t(11;18) involving the API2/MLT genes, has not been demonstrated in primary cutaneous MZL,[157,158] but the

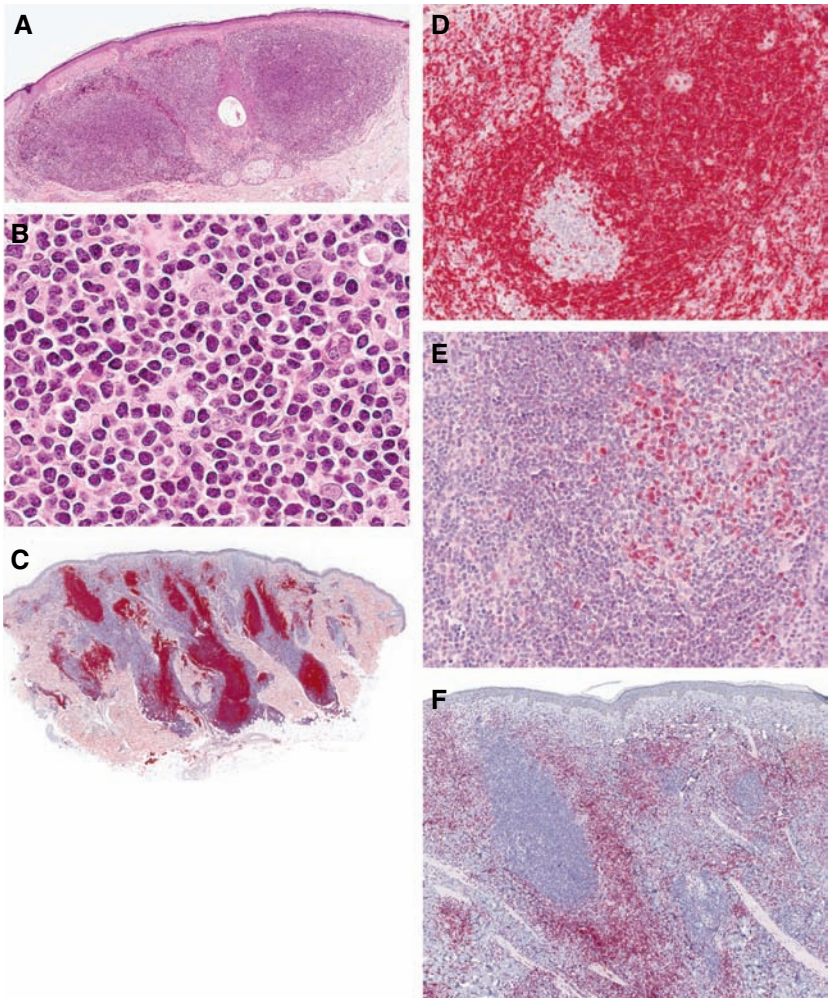

Fig. 11. A) Primary cutaneous marginal zone B-cell lymphoma (MZL): Superficial and deep nodular infiltrate, showing paler zone around darker central areas. Germinal centers are invaded by tumor cells. No epidermotropism (grenz zone). B) Primary cutaneous MZL: infiltrate of small lymphocytes with slight nuclear atypia (monocytoid aspect). C) Primary cutaneous MZL: low magnification shows $CD20^+$ infiltrate surrounded by $CD20^-$ T-cell population. D) Primary cutaneous MZL: strong positivity of the tumor cells for bcl-2 and remnants of germinal centers are negative. E) Primary cutaneous MZL: bcl-6 shows inverse reaction to bcl-2: remnant ot the germinal center is positive, cells of marginal zone are negative. F) Primary cutaneous MZL: the centers are $CD3^-$, surrounded by population with $CD3^+$ cells.

t(14;18)(q32;q21) translocation involving IGH and MALT1 was reported in approximately one-third of cases.[158] Fas gene mutations are present in a minority of cases, similar to MZL of other extranodal sites. Abnormalities of bcl-10 are absent.[159]

Primary cutaneous follicle center lymphoma

Synonyms in other classifications

WHO/EORTC classification (2005): primary cutaneous follicle center lymphoma
WHO classification (2001): cutaneous follicle center lymphoma
REAL classification (1997): follicle center lymphoma, follicular
EORTC classification (1997): primary cutaneous follicle center cell lymphoma

Follicle center lymphoma (FCL) and MZL are the most common types of primary cutaneous B-cell lymphomas. In contrast to MZL, FCL shows a predilection for the scalp, forehead, and trunk.[160–162] Synonyms for follicular lymphoma include reticulohistiocytoma of the back or Crosti lymphoma.[163] Three growth patterns can be differentiated: follicular, follicular and diffuse, and diffuse. The most important differential diagnoses include follicular pseudolymphoma (or reactive lymphoid hyperplasia), MZL, and diffuse large B-cell lymphoma. In contrast to nodal FCL, primary cutaneous FCLs have a favorable prognosis with 5-year-survival rates over 90%. They share their biologic behavior with other extranodal forms of FCL as shown recently by Goodlad and coworkers.[164]

Histology

Primary cutaneous FCL is defined as a neoplasm with differentiation of follicle center cells (centrocytes and centroblasts) displaying a follicular, follicular and diffuse or a diffuse growth pattern. Grading of primary cutaneous FCL as in its nodal counterpart based on the proportion of centroblasts (Grades 1–3) is not prognostically relevant.

FCL shows a nodular or diffuse infiltrate within the dermis, often extending into the subcutaneous tissue (Fig. 12A), and contains a mixture of

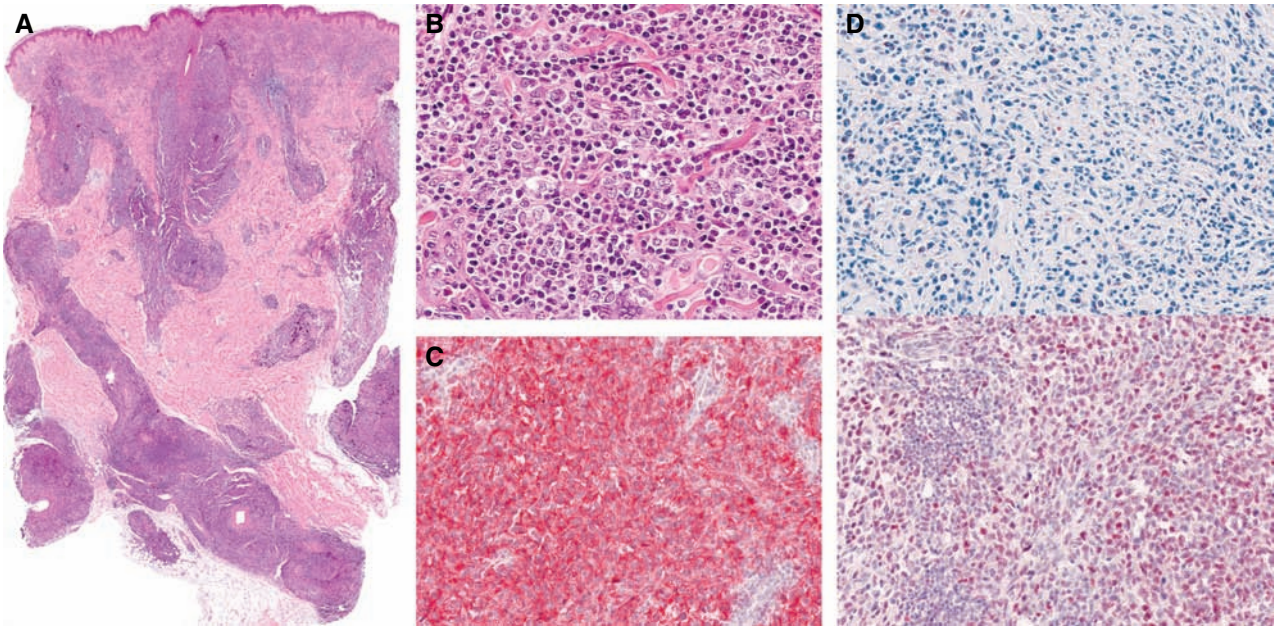

Fig. 12. A) Primary cutaneous Follicle center lymphoma (FCL): scanning magnification shows dense nodular lymphoid infiltrate. B) Primary cutaneous FCL: the infiltrate consists of centrocyte-like and centroblast-like tumor cells. C) Primary cutaneous FCL: expression of CD20 by tumor cells. D) Primary cutaneous FCL: the cells are bcl-2^- (top) and bcl-6^+ (bottom).

centrocytes and centroblasts (Fig. 12B) with variable growth patterns, and may be follicular, follicular and diffuse, or diffuse. In most cases, there is a subepidermal Grenz zone. In contrast to the polymorphous follicular composition in reactive infiltrates (pseudolymphoma or lymphoid hyperplasia) characterized by an admixture of centrocytes, centroblasts, immunoblasts, and tingible body macrophages,[165] neoplastic follicles in FCL show a relatively monomorphic cellular composition with a low number of mitoses, no or only few tingible body macrophages and lack of starry sky features.[166]

Immunophenotype

The cells express B-cell markers and are $CD19^+$, $CD20^+$, $CD22^+$, $CD79a^+$, $CD5^-$, $CD23^{+/-}$, and CD43 (Fig. 12C).[165] CD10 is variably expressed (often positive in follicular cases and more frequently negative in lesions with diffuse pattern of growth). Interfollicular $CD10^+$ blasts may be present singly or in clusters in follicular cases. Tumor cells express bcl-6 and in most cases are negative for bcl-2 (Fig. 12D).[167] The MUM/IRF4 antigen, which is positive in diffuse large B-cell lymphoma, is not expressed in FCL. Monotypic staining for surface immunoglobulins (sIg) is more often seen in cryostat sections. Absence of detectable sIg staining is common in tumors showing a diffuse population of large follicular center cells. A major difference between primary and secondary follicular lymphoma involving cutaneous sites is the presence of the bcl-2 translocation, which is usually present in 75–95% of nodal follicular lymphomas. It is less often found in primary cutaneous FCL.[167] This discrepancy has led to speculation that primary cutaneous FCL may be a separate disease. The follicles are associated with FDCs and are positive for CD21, CD23, and CD35. Residual, scattered FDC may be sometimes found in diffuse large-cell infiltrates. Neoplastic cells are constantly $CD5^-$ and $CD43^-$. Admixed T cells may be abundant and sometimes dominant, particularly in small, early lesions.

Molecular findings and genetics

Clonally rearranged immunoglobulin genes can be regularly detected. Bcl-2 gene rearrangement and t(14;18) chromosomal translocation are absent in most cases.[167–170] In systemic B-cell lymphoma, inactivation of p15(INK4b) and p16(INK4a) is frequently observed and may be associated with a poor prognosis. In primary cutaneous B-cell lymphoma, p15(INK4b) and p16(INK4a) biallelic gene abnormalities are common, most frequently as a result of promoter hypermethylation.[171] In a minority of primary cutaneous FCL, chromosomal imbalances have been identified by CGH analysis, but a consistent pattern has not been emerged.[173,173] Storz and colleagues[174] were the first to analyze expression profiles of primary cutaneous B-cell lymphoma; the FCL samples group well together, implying that these tumors share a similar overall gene-expression pattern and arise from germinal center cells.

Cutaneous diffuse large B-cell lymphoma (DLBCL)

Synonyms in other classifications

WHO/EORTC classification (2005): cutaneous diffuse large B-cell lymphoma
WHO classification (2001): diffuse large B-cell lymphoma
REAL classification (1997): diffuse large B-cell lymphoma
EORTC classification (1997): primary cutaneous large B-cell lymphoma of the leg

Primary cutaneous diffuse large B-cell lymphomas (PCDLBCL) are composed of large B cells (centroblasts and immunoblasts).[175,176] Two forms of primary cutaneous LBCL are distinguished in the WHO-EORTC Consensus classification: DLBCL, leg-type and DLBCL, other. The most common variant, DLBCL, leg-type, usually occurs on the leg and less frequently at other sites. Other variants are referred to as DLBCL, other and comprise T-cell/histiocyte-rich DLBCL, plasmablastic lymphoma and others that do not fulfill the criteria for a DLBCL, leg-type. In former classifications, some of these variants might have been referred to as centroblastic lymphoma, immunoblastic lymphoma, reticulohistiocytoma of the dorsum (Crosti disease), anaplastic large-cell B-cell lymphomas, multilobate large B-cell lymphomas, and still other names.

Diffuse large B-cell lymphoma (DLBCL), leg-type

Histology

A diffuse growth pattern is found with an monomorphous infiltrate involving the entire dermis. Adnexal structures are usually destroyed (Fig. 13A). The infiltrate may extend into subcutaneous tissue. The epidermis is often spared with a Grenz zone. The infiltrate is composed of monomorphic medium-sized to large B cells resembling centroblasts with large non-cleaved nuclei and nucleoli attached to the nuclear membrane, or immunoblasts with a large vesicular nucleus and a prominent centrally placed nucleolus (Fig. 13B). In contrast to FCL, centrocytes are absent. Mitotic figures can frequently be detected. The nuclei are predominantly round with coarsely clumped chromatin. There is usually a minimal inflammatory component and little stromal reaction.

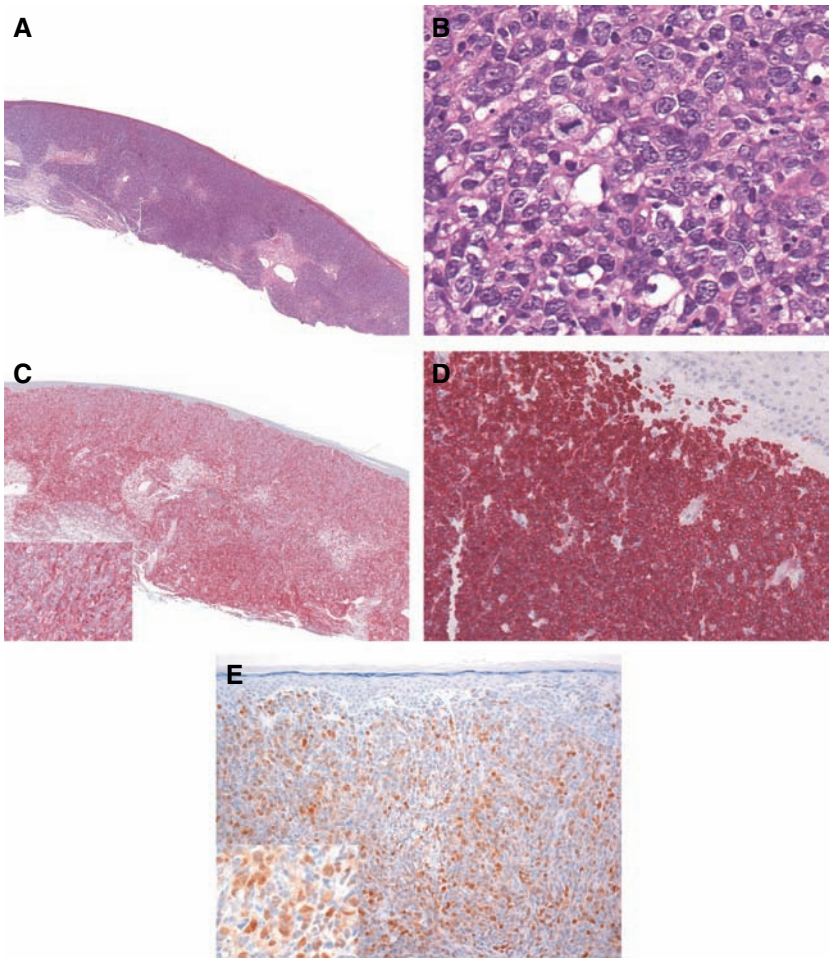

Fig. 13. A) Primary cutaneous diffuse large B-cell lymphoma (DLBCL): dense, monomorphous lymphoid infiltrate through the dermis; adnexa are destroyed. B) Primary cutaneous DLBCL: infiltrate of large lymphoid cells with coarse chromatin and high mitotic activity resembling mostly centroblasts. C) Primary cutaneous DLBCL: strong CD79a positivity throughout the tumor; inset shows high mitotic activity. D) Primary cutaneous DLBCL: strong bcl-2 positivity of tumor cells. E) Primary cutaneous DLBCL: Strong positivity of tumor cells for Mum-1.

Immunophenotype

The tumor cells express CD19$^+$, CD20$^+$, CD22$^+$, and CD79a$^+$ (Fig. 13C), and CD5$^-$, CD10$^-$, and CD138$^-$, cyclin D1$^-$. Bcl-6 is variably expressed but mostly positive. Deletion or promoter region hypermethylation of the p16INK4a gene was detected in two patients with DLBCL. Loss of B-cell markers also occurs.[177] The strong positivity for Bcl-2 protein (Fig. 13D) and MUM-1/IRF4[178] (Fig. 13E) is an important feature of this type of lymphoma, independent from the localization, leg or other sites, distinguishing this entity from FCL with diffuse growth pattern (Table 3). These immunophenotypic features have been shown in nodal DLBCL to correlate with an activated B-cell gene-expression profile, which is usually predictive of an aggressive clinical course.[179] Among all primary cutaneous large B-cell lymphomas, Bcl-6$^+$ and MUM-1 cases had a better overall survival than Bcl-6$^-$, MUM-1$^+$ cases (176 vs. 26 months).[180] In the group of DLBCL leg type, MUM-1 is not a prognostic marker.

Molecular findings and genetics

The immunoglobulin genes are clonally rearranged. The t(14;18) can be detected in secondary cutaneous large B-cell lymphomas but not in primary cutaneous diffuse large B-cell lymphomas. Expression of p53 protein missense or loss-of-function mutations in the p53 gene may be found in some patients The bcl-2/JH translocation is absent.[181–183] Significant differences have not been identified among tumors of the leg-type arising in different sites.[178,182]

In a study of gene expression profiles by Storz et al.,[174] analysis of arrays shows that primary cutaneous DLBCL cluster is adjacent to FCL samples, whereas secondary cutaneous DLBCL cases are removed from these two groups, suggesting that they are biologically and molecularly distinct. There is a characteristic B-cell germinal center (GC) signature in tonsil, primary and secondary cutaneous FCL, and in primary cutaneous DLBCL, suggesting that these diseases are more closely related than expected from earlier histological and immunohistological analyses. In contrast, secondary cutaneous DLBCL lacked the expression of B-cell GC signature. Plasma cell signature on the other side could be identified in two of five MZL with prominent plasmacytoid differentiation. Subsequently, Hoefnagel and colleagues[184] studied gene-expression profiles of eight primary cutaneous FCL with a diffuse large-cell histology and 13 pcDLBCLs-leg using Affymetrix oligonucleotide arrays. The pcDLBCL-leg lymphoma presented an 'activated B cell' ABC-like DLBCL expression pattern, the primary cutaneous FCL a 'germinal center B' GCB-like DLBCL transcription signature, as defined by Wright et al.[185] The transcript with the greatest variation was SPINK2, whose function still remains to be elucidated. It is highly expressed in FCL, but absent or only very low in pcDLBCL leg type samples. Consistent with previous studies,[155] strong Bcl-2 protein expression was found in almost all pcDLBCL leg type, but not in the FCL. In recent years, staining for bcl-2, bcl-6, and CD10 has become the standard marker set for differential diagnosis of cutaneous B-cell LPD as depicted in Table 3. Additionally, MUM1/IRF4 seems to be of value for delineating DLBCL with poorer outcome. MUM1/IRF4 has been suspected to play a role in the progression of B-cell lymphoma/leukemia by regulating the expression of various genes including the monokine induced by interferon-gamma.[186] In systemic DLBCL, cases with coexpression of survivin and T332 have a significantly worse prognosis than single-positive and double-negative cases, and so survivin and the novel monoclonal antibody, T332, might be of prognostic value for this group. High levels of caspase 3 and absence of p16 expression in pcDLBCL also indicate a poor prognosis.[187]

The pathologic, immunophenotypic and molecular features of primary cutaneous large B-cell lymphoma of the leg and at other sites indicate that they are similar both with morphofunctional and molecular profiles, and therefore it is justified to refer to altogether as DLBCL, leg-type in analogy to similar terms in the classification of lymphomas such as nasal type.

Table 3. Summary on phenotypical features of cutaneous B-cell lymphomas and pseudolymphomas

	Bcl-2	Bcl-6	CD10	(14; 18)	MUM1/IRF4
MZL/ICY	+	–	–	–	–
FCL	–	+	+/–	–	–
Secondary FCL	+	+	+	+	–
DLBCCL	+	+	–	–/+	+
PSL	–	+	+	–	–

MZL/ICY, marginal zone lymphoma/immunocytoma; FCL, follicle center lymphoma; Secondary FCL secondary cutaneous FCL; DLBCL, diffuse large B-cell lymphoma; PSL, pseudolymphoma or reactive lymphoid hyperplasia. The term pseudolymphoma is used by dermatologists as a synonym for any type of reactive infiltrate in the skin that is extensive enough to cause a tumor or nodule.

Diffuse large B-cell lymphoma, other

This term refers to other lymphomas showing a diffuse growth pattern, composed of large transformed B-cells that lack the typical features of DLBCL, leg-type and do not conform to the definition of primary cutaneous FCL with diffuse growth pattern. These tumors contain a monomorphic population of centroblast-like cells and often present

with a mixed inflammatory background. Bcl-2 protein may be negative, whereas bcl-6 will usually be expressed.

T-cell/histiocyte-rich diffuse large B-cell lymphoma

This rare variant of a DLBCL is defined by the predominance of non-neoplastic T cells admixed with scattered large tumoral B cells.[188]

Histology

There are a few large pleomorphic cells with clear cytoplasm and multilobular nuclei resembling Hodgkin or Reed–Sternberg cells scattered within a background of reactive small T lymphocytes (>75%) (Fig. 14), some of which have irregular nuclear contours, epithelioid histiocytes, and plasma cells. Centroblasts and immunoblasts can be observed. There may be a marked vascular proliferation in some cases.[188,189]

Immunophenotype

The large neoplastic cells express pan-B-cell antigens CD19 (Fig. 14), CD22, and CD79a, with light-chain restriction, but are negative for CD15 and CD30, which excludes Hodgkin lymphoma. The reactive small-cell population represents T-helper cells but small reactive B cells can also be found.[190] Due to the lower number of tumor cells, detection of IgH gene rearrangements may be difficult to assess in some cases.

Intravascular large B-cell lymphoma (IVL)

Synonyms in other classifications

WHO/EORTC classification (2005): intravascular large B-cell lymphoma
WHO classification (2001): intravascular large B-cell lymphoma (IV-LBL)
REAL classification (1997): diffuse large B-cell lymphoma
EORTC classification (1997): intravascular large B-cell lymphoma (provisional entity)

Intravascular lymphoma is a rare highly malignant large-cell lymphoma with systemic spread, characterized by the presence of tumor cells in the lumina of small vessels, particularly capillaries and venules. The skin and the nervous system are preferential sites of primary manifestation. The tumor cells express B-cell markers in the vast majority of cases; rarely a T-cell phenotype is found. Other synonyms include systemic angioendotheliomatosis,[191] intravascular lymphomatosis, and Tappeiner–Pfleger syndrome. Neoplastic angioendotheliomatosis has to be differentiated from reactive angioendotheliomatosis, which may develop in conjunction with a variety of underlying systemic inflammatory or neoplastic diseases.[192,193] Patients with disease limited to the skin (cutaneous variant) have a significantly better outcome than the other patients with IVL.[194]

Histology

The microscopic features are pathognomonic showing a dense proliferation of atypical large lymphoid cells with round or oval nuclei within the lumina of capillaries and postcapillary venules[195,196] (Fig. 15). Tumor cells are large with vesicular nuclei, prominent nucleoli, and frequent mitoses. Partial occlusion of vessels by tumor cells and fibrin thrombi results in the clinical features of reticular erythema and livedo reticularis. Extravascular involvement may occur.[197]

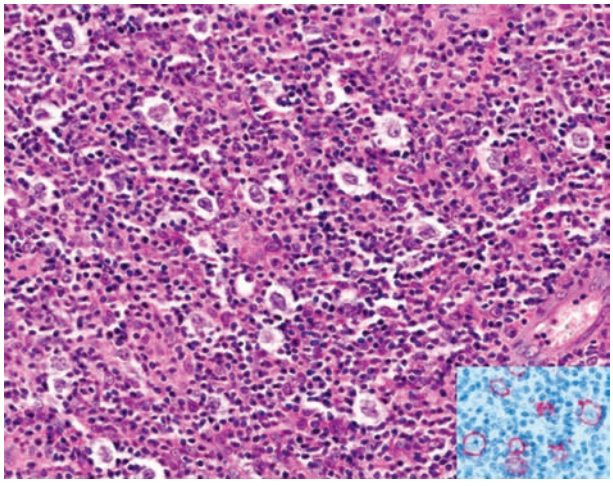

Fig. 14. T cell-rich B-cell lymphoma (BCL): detail of the infiltrate consisting of many reactive T lymphocytes (smaller cells) and scattered large blastic B cells. Inset: large cells are positive for CD20.

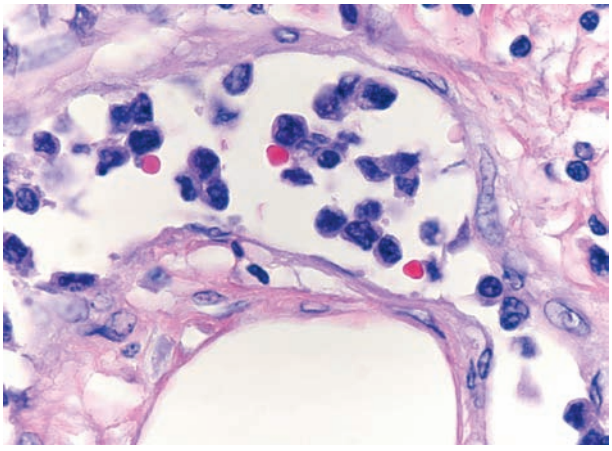

Fig. 15. Intravascular large B-cell lymphoma: large atypical blastic B cells intravascularly.

Immunophenotype

Tumor cells usually express B-cell-associated antigens and may coexpress CD10 or CD5,[198,199] CD11a, and CD49d (VLA-4).[200] Most IVLs overexpress bcl-2 protein.[197] Rare cases with a T-cell phenotype have been described. There is no bcl-2 gene rearrangement.[25,201,202] These cases have to be distinguished from other intravascular lymphomas of different lineages.[203–205] A defect in homing receptors and adhesion molecules on the neoplastic cells and the endothelial cells has been suggested to be responsible for the intravascular trapping of lymphoid tumor cells.[206,207] However, the precise mechanisms of lymphoid–endothelial interaction leading to vascular occlusion and thrombotic events are not clear.

Molecular findings and genetics

Rearrangements of IgH family genes is seen in IVL. Structural aberrations in chromosomes 1, 6, and 18, especially 1p and trisomy 18, have been found in some cases.[208] Mutations of p53, p16, and p21 genes do not seem to be involved with IVL cells.[209] CD29 (beta1 integrin subunit), CD43 (leukosialin), CD44 (H-CAM), CD54 (ICAM-1), embryonal N-CAM (e-NCAM), and episialin are molecules known to be involved in lymphocyte and endothelial adhesion processes.[207] In IVL, the intravascular neoplastic lymphocytes express CD44 but are negative for CD29 and for CD54. The absence of CD29 and CD54 in IVL may contribute to the intravascular and disseminated distribution pattern.[207]

Blastic NK-cell lymphoma or CD4$^+$/CD56$^+$ hematodermic neoplasm

Synonyms in other classifications

WHO/EORTC classification (2005): CD4$^+$/CD56$^+$ hematodermic neoplasm; blastic NK-cell lymphoma
WHO classification (2001): blastic NK-cell lymphoma
REAL classification (1997): not listed
EORTC classification (1997): not listed

Although the cell of origin is not yet completely elucidated, the immunophenotypic profile (CD4$^+$, CD56$^+$, and CD123$^+$) suggests that the tumor cells represent most probably precursor cells related to activated plasmacytoid monocytes.[210] Cytogenetically, they are related to myeloid and to lymphoid precursor cells (type 2 dendritic cells).

Skin involvement occurs in 87% of the patients and manifests with contusiform, brownish infiltrated plaques or nodules.[211,212] The oral mucosa is commonly involved.

Histology

Histologically, monomorphous, non-epidermotropic medium-to-large-sized tumor cells with round or pleomorphic nuclei form a diffuse dense infiltrate throughout the dermis, separated from the epidermis by a small Grenz zone (Fig. 16). Erythrocyte extravasation is a characteristic feature, explaining the bruise-like appearance.

Immunophenotype

The cells express CD4, CD56, CD123 and TCL-1 but are negative for other T-, B-, NK-cell, or myeloid markers. In contrast myelomonocytic neoplasms coexpresses CD43 and CD74 in addition to myeloid markers (CD13, CD15, myeloperoxidase, and lysozyme). A minority of tumor cells in some cases also may express CD68 or TdT.[213]

Molecular findings and genetics

Because the tumor cells are not related to T-cells, there is no clonal rearrangement of TCR genes.

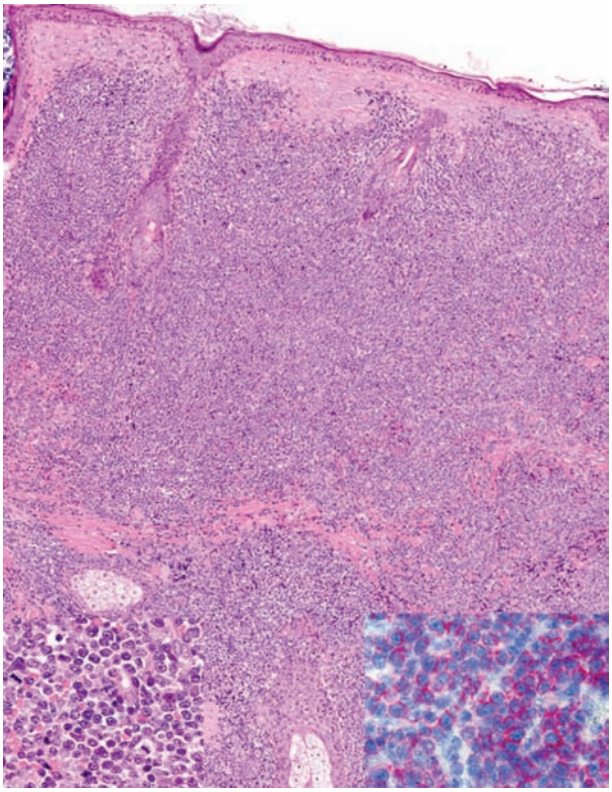

Fig. 16. Blastic natural killer-cell lymphoma: dense diffuse infiltrate throughout the dermis, sparing the grenz zone; left inset: large blastic cells with coarse chromatin, nucleoli and high mitotic activity; right inset: CD56$^+$ tumor cells.

Conclusions

Because the microscopic studies of Xavier Gillot (1842–1910) and Louis Antoine Ranvier (1835–1922) in Paris indicated that MF was caused by regeneration of lymphoid tissue in the skin and that MF had to be considered as a cutaneous manifestation of lymphoma–lymphadénie cutanée,[214] there has never been a reason for classifying cutaneous lymphomas differently from lymphomas at other sites with same pathogenetic background. The new WHO/EORTC classification of cutaneous lymphomas, which employs a terminology compatible with systemic lymphomas but also reflects the organ-specific pecularities of cutaneous lymphomas.

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