Cutaneous Lymphomas: from Morphology to Chip Technology

L. Cerroni and T. Wiesner
Department of Dermatology. Medical University of Graz. Austria.

Abstract. Cutaneous lymphomas represent a heterogenous group of malignant lymphoid diseases with particular tropism for the skin. Prognosis and treatment depend on the type of lymphoma, thus precise diagnosis and classification are of paramount importance. Classification of cutaneous lymphomas relies on a synthesis of all available information, including clinical history and presentation, histopathology, immunophenotype, and molecular data. Thanks to the efforts of the lymphoma groups of both the World Health Organization (WHO) and the European Organization for Research and Treatment of Cancer (EORTC), a joint WHO-EORTC classification for primary cutaneous lymphomas has been proposed in 2005. The WHO-EORTC classification has been adsorbed with minor changes in the 2008 WHO classification of tumours of haematopoietic and lymphoid tissues, thus including for the first time primary cutaneous lymphomas as distinct subtypes of extranodal lymphomas in a general classification of lymphomas.

Key words: cutaneous lymphomas, mycosis fungoides, cutaneous B-cell lymphoma, cutaneous T-cell lymphoma.

Mycosis fungoides, the prototype and most common form of cutaneous lymphoma, has been described over two centuries ago. Most of the progress in this particular field of dermatologic oncology, however, has been achieved in the last 10–20 years, thanks to the introduction of ancillary techniques such as immunohistochemistry and molecular biology that helped to better diagnose and classify these disorders, and to unravel the pathogenetic events at their base. Besides mycosis fungoides, many other types of cutaneous lymphomas have been well characterized in the recent past, and the skin is now recognized as one of the main sites of onset of extranodal non–Hodgkin lymphomas.

The first widely accepted classification of primary cutaneous lymphomas (that is, lymphomas arising in the skin with no extracutaneous disease at presentation) has been published by the European Organization for Research and Treatment of Cancer (EORTC) – Cutaneous Lymphoma Project Group in 1997. An update was subsequently published by the EORTC together with the World Health Organization (WHO) in 2005. This WHO-EORTC classification has been included with only minor changes in the new 2008 WHO Classification of Tumours of Haema-
to lymphocyte and Lymphoid Tissues (table 1). In the following, we will summarize some important aspects of cutaneous lymphomas, focusing on advances in the diagnosis and understanding of the most relevant among these diseases.

### Mycosis Fungoides and Variants

The term mycosis fungoides is now restricted to the characteristic disease progressing slowly through patch-plaque- and tumor-stages (Alibert-Bazin type) (fig. 1). The so-called “mycosis fungoides a tumeur d’emblée” and other aggressive variants presenting with ulcerated plaques and tumors from the onset (for example generalized pagetoid reticulosis– Ketron-Goodman type) are now classified within the group of aggressive cytotoxic natural killer (NK)/T-cell lymphomas and separated from classic mycosis fungoides.

In spite of over two centuries of research, the diagnosis of mycosis fungoides is still based mainly on clinicopathologic correlation (fig. 2). Immunohistology and molecular biology play yet a limited role in the diagnosis of early lesions. Controversies on the definition of early lesions, on the other hand, still abound, and the debate on the so-called “para-

---

**Table 1. Comparison of the WHO-EORTC classification of cutaneous lymphomas (2005) with the WHO classification of tumors of hematopoietic and lymphoid tissues (2008)**

<table>
<thead>
<tr>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Cutaneous T- and NK-cell lymphomas</td>
<td></td>
</tr>
<tr>
<td>Mycosis fungoides</td>
<td>Mycosis fungoides</td>
</tr>
<tr>
<td>MF-variants</td>
<td></td>
</tr>
<tr>
<td>Pilotropic MF</td>
<td></td>
</tr>
<tr>
<td>Pagetoid reticulosis</td>
<td></td>
</tr>
<tr>
<td>“Granulomatous slack skin”</td>
<td></td>
</tr>
<tr>
<td>Sézary syndrome</td>
<td>Sézary syndrome</td>
</tr>
<tr>
<td>Adult T-cell lymphoma/leukemia</td>
<td>Adult T-cell lymphoma/leukemia</td>
</tr>
<tr>
<td>Primary cutaneous CD30+ lymphoproliferative diseases</td>
<td>Primary cutaneous CD30+ lymphoproliferative diseases</td>
</tr>
<tr>
<td>Primary cutaneous anaplastic large T-cell lymphoma</td>
<td>Primary cutaneous anaplastic large T-cell lymphoma</td>
</tr>
<tr>
<td>Lymphomatoid papulosis</td>
<td>Lymphomatoid papulosis</td>
</tr>
<tr>
<td>Subcutaneous panniculitis-like T-cell lymphoma</td>
<td>Subcutaneous panniculitis-like T-cell lymphoma</td>
</tr>
<tr>
<td>Extranodal NK/T-cell lymphoma, nasal type</td>
<td>Extranodal NK/T-cell lymphoma, nasal type</td>
</tr>
<tr>
<td>Primary cutaneous peripheral T-cell lymphoma, unspecified</td>
<td>Primary cutaneous peripheral T-cell lymphoma, unspecified</td>
</tr>
<tr>
<td>Primary cutaneous aggressive epidermotropic CD8+ T-cell lymphoma</td>
<td>Primary cutaneous aggressive epidermotropic CD8+ T-cell lymphoma</td>
</tr>
<tr>
<td>Cutaneous gamma/delta T-cell lymphoma</td>
<td>Cutaneous gamma/delta T-cell lymphoma</td>
</tr>
<tr>
<td>Primary cutaneous CD4+ small/medium pleomorphic T-cell lymphoma</td>
<td>Primary cutaneous CD4+ small/medium pleomorphic T-cell lymphoma</td>
</tr>
<tr>
<td>Cutaneous B-cell lymphomas</td>
<td></td>
</tr>
<tr>
<td>Primary cutaneous marginal zone lymphoma</td>
<td>Extranodal marginal zone lymphoma of the “mucosa-associated lymphoid tissue” (MALT-lymphoma)</td>
</tr>
<tr>
<td>Primary cutaneous follicle center lymphoma</td>
<td>Primary cutaneous follicle center lymphoma</td>
</tr>
<tr>
<td>Primary cutaneous diffuse large B-cell lymphoma, leg type</td>
<td>Primary cutaneous diffuse large B-cell lymphoma, leg type</td>
</tr>
<tr>
<td>Primary cutaneous diffuse large B-cell lymphoma, others</td>
<td>Intravascular large B-cell lymphoma</td>
</tr>
<tr>
<td>Intravascular large B-cell lymphoma</td>
<td></td>
</tr>
<tr>
<td>Precursor hematological neoplasm</td>
<td></td>
</tr>
<tr>
<td>CD4+/CD56+ hematodermic neoplasm</td>
<td>Blastic plasmacytoid dendritic cell neoplasm</td>
</tr>
</tbody>
</table>

*Only primary cutaneous entities.
psoriases” is far from being settled. In this context, some analogies with other cutaneous cancers as well as with extracutaneous lymphomas may allow to better understand the mycosis fungoides vs. parapsoriasis controversy:

1. We know today very well that not all forms of early cancer progress to invasive and metastatic disease. Actinic keratosis represents an early stage in the evolution of some cutaneous squamous cell carcinomas, but not
all actinic keratoses progress to invasive carcinoma; the same applies for other tumors, including early stages of melanoma in situ.

2. Monoclonal gammopathy is considered a prototype of “premalignant” lymphoid dyscrasias; although only a percentage of patients with monoclonal gammopathy progresses to overt lymphoma (multiple myeloma); two recent studies showed that almost all patients with multiple myeloma had a monoclonal gammopathy before developing the lymphoma.

In a similar way, although not all patients with parapsoriasis progress to mycosis fungoides, most patients with mycosis fungoides have a long history of self-resolving, recurrent “eczematous” conditions before the diagnosis is made. In this context, we believe that parapsoriasis en plaques (a misnomer, as the lesions are patches) represents a precursor (or early stage) of mycosis fungoides.

Recent developments showed that some peculiar variants of mycosis fungoides, formerly considered different types of lymphoma or even benign conditions, belong indeed to the spectrum of the disease. In particular, there is now sufficient evidence to state that “syringolymphoid hyperplasia with alopecia” is a syringotropic variant of mycosis fungoides characterized by prominent involvement of the eccrine glands with syringometaplasia and often with concomitant pilotropism and follicular mucinosis (fig. 3). Other recently described clinicopathologic variants include a papular form of the disease.

Immunophenotypic analyses of early patches of mycosis fungoides do not provide diagnostic clues, although epidermotropic lymphocytes may be visualized better with stainings for T-cells. A cytotoxic phenotype may be observed in early mycosis fungoides, but recent data suggest that this finding has no prognostic implications. On the other hand, the finding of a cytotoxic phenotype in otherwise conventional patches of mycosis fungoides demonstrates the overlapping clinicopathologic features of cutaneous lymphomas, as different entities may show similar aspects. A precise classification is sometimes very difficult and only possible upon the synthesis of clinical history, clinical presentation, histopathology and immunophenotype.

The diagnostic utility of the analysis of T-cell receptor (TCR) genes rearrangement in early cases of mycosis fungoides is yet limited, as a clonal rearrangement can be found only in a variable proportion of cases, possibly depending upon the number of tumor cells and the detection technique employed. A recent study applied simultaneously gene expression analysis and array-based comparative genomic hybridization to investigate 22 patients with tumour stage mycosis fungoides. Gains of 7q36, 7q21-7q22, 7q32-7q35, and 7q11.2 were observed in more than 50% of cases. Losses were most frequently observed at 9p21, 13q14-13q31, and 5q13. These genomic aberrations are observed far less frequently in Sézary syndrome, suggesting that the molecular pathogenesis, and therefore also the therapeutic requirements, may be different. Related to the frequently gained regions, an increased gene expression of \textit{EASTK} (7q36) and \textit{SKAP1} (7q21) was demonstrated, as well as a diminished expression of \textit{RB1} and \textit{DLEU1} related to the recurrent loss of 13q14-13q31. These results indicate that gene dosage influences transcript abundance of these tumor-related genes. Chromosomal alterations of 9p21 (which includes the \textit{CDKN2A} gene), 8q24, and 1q21-1q22 were associated with poor prognosis. In subgroups of patients with mycosis fungoides, mutations and losses affecting the \textit{CDKN2A}, \textit{FAS}, and \textit{JUNB} genes have been identified. A constitutive activation of \textit{STAT3}, mutation of \textit{TP53}, and deletion of \textit{PTEN} have been linked to late disease stages and may be associated with disease progression. In advanced stages, multiple and complex structural and numerical abnormalities are present in most patients, suggesting a high grade of genomic instability.
At present, translation of these molecular data into clinical practice (diagnosis, assessment of prognosis, treatment) has not yet been achieved. In particular, results on early lesions of the disease are still largely lacking, possibly due to the difficulties in obtaining sufficient tumor DNA from early patches of the disease. The detection of a clone of T lymphocytes in lesional skin at first diagnosis of early mycosis fungoides does not have prognostic implications, but the presence of the same clone in repeated biopsies over time may be associated with higher risk of progression to more advanced stages.

**Sézary Syndrome**

The new WHO classification separates Sézary syndrome from mycosis fungoides, considering it a distinct entity of cutaneous T-cell lymphoma. This distinction is supported by the finding that aberrations of chromosome 8, 10, 17, which are commonly found in Sézary syndrome, occur only in about 25% of cases of tumor-stage mycosis fungoides. Conversely, the malignant T-cells of mycosis fungoides frequently show gains of the chromosomal regions 1 and 7 and losses on chromosome 8. Gains of 7q are observed in more than 50% of mycosis fungoides patients, but are detected only in about 15% of Sézary syndrome cells. These findings argue against the notion that differences between these lymphomas are only a matter of stage, and strongly suggest that the molecular pathogenesis of mycosis fungoides and Sézary syndrome follows distinct pathways.

The criteria for diagnosis of Sézary syndrome are still controversial. Besides the typical finding of erythroderma, generalized lymphadenopathy and presence of malignant circulating cells, for diagnosis, an absolute cell count of >1000 cells per mm$^3$, an expanded CD3+ population of T-cells resulting in a CD4/CD8 ratio of >10 and/or the loss of one or more T-cell antigens should be demonstrated. When these strict criteria are met, Sézary syndrome is a rare disease, and prognosis is very poor (5-year survival rate of 10–20%).

Complex rearranged karyotypes with several numerical and structural unbalanced aberrations are common in Sézary syndrome and suggest a high grade of genomic instability. A recent study investigated the malignant T cells from 20 patients using array-based comparative genomic hybridization. The overall pattern of chromosomal aberrations was characterized by gains on chromosome 17 and 8, as well as losses on chromosome 10. The highly recurrent aberrations included gains of 17q23-25 and 8q24 and loss of 17p13, and were detected in about 75% of patients. Additional evaluation of candidate oncogenes and tumor suppressor genes, residing in loci with chromosomal aberrations, pointed to dysregulation of the MYC oncogene or of their regulating genes, to losses of TP53 and genome maintenance genes, and to an activation of interleukin 2 (IL-2) receptor signaling pathway components. As for mycosis fungoides, these results did not yet find a translation into clinical practice, but are of great importance for further understanding of the disease and for setting the stage for future trials.

**CD30+ Cutaneous Lymphoproliferative Disorders**

One of the major changes in the classification of cutaneous lymphomas in the last 10 years concerned lymphomatoid papulosis and primary cutaneous anaplastic large cell lymphoma, which today are considered as part of a spectrum rather than as separate entities. The notion that dermatopathologists could confidently classify a given case as lymphomatoid papulosis or primary cutaneous anaplastic large cell lymphoma has been replaced by the recognition that such a distinction is possible only upon clinical grounds, as both diseases present overlapping histopathologic and phenotypic features. In spite of promising reports of the value of single antibodies for differentiating of lymphomatoid papulosis from primary cutaneous anaplastic large cell lymphoma (i.e., MUM-1), there is no antibody or set of markers that allows that distinction to be made. Thus, clinicopathologic correlation is of paramount importance for the precise classification of these lesions. In this context, we would like to underline that CD30 is one of the least specific immunohistochemical markers, and that a diagnosis of cutaneous CD30+ lymphoproliferative disorder can be made only upon compelling clinicopathologic evidence and complete phenotypic analyses.

Identical TCR rearrangements have been detected in lymphomatoid papulosis lesions and associated lymphomas (mycosis fungoides, anaplastic large cell lymphoma), suggesting a clonal relationship of the diseases in the same patient. Translocations involving the ALK gene at chromosome 2 are not detected in lymphomatoid papulosis, and no specific genetic aberrations have been reported so far.

Clonally rearranged TCR genes have been detected in most cases of primary cutaneous anaplastic large cell lymphoma, but the TCR proteins are often not expressed. Comparative genomic hybridization demonstrated copy number gains of several oncogenes, but no consistent genetic abnormality has been identified. Amplification of JUNB was observed in 7 of 10 primary cutaneous anaplastic large cell lymphomas. The translocation of the ALK gene, which is frequently detected in systemic anaplastic large cell lymphoma, is not found in the primary cutaneous form of the disease, again pointing at the differences between cutaneous and extracutaneous lymphomas.
Subcutaneous Panniculitis-Like T-Cell Lymphoma

This is one of the cutaneous lymphomas which has been redefined in the last few years. In the past, this entity included an heterogeneous group of diseases ranging from alfa/beta T-cell lymphomas and gamma/delta T-cell lymphomas to NK/T-cell lymphomas. Today the term is strictly confined to a disease characterized by the proliferation of alfa/beta cytotoxic T lymphocytes (positive for CD3, CD8, beta-F1, TIA-1, and granzyme B, and negative for CD4, CD30, and CD56, as well as for Epstein-Barr virus-EBV). When this strict definition is applied, the disease has a good prognosis with a 5-year survival of greater than 80%.

Interestingly, recent studies pointed at a possible relationship of subcutaneous panniculitis-like T-cell lymphoma with autoimmune diseases, particularly with lupus erythematosus. This is of particular importance for dermatologists and dermatopathologists because the main clinical and histopathologic differential diagnosis of subcutaneous panniculitis-like T-cell lymphoma is with lupus panniculitis (fig. 6). Thus, the concept of a possible relationship between the two diseases may imply a complete shift of perspective for what concerns the differential diagnosis.

In cases of a suspect diagnosis of subcutaneous panniculitis-like T-cell lymphoma, complete phenotypic analyses should be performed, including at least antibodies for the alfa/beta chain of the T-cell receptor (antibodies for the gamma/delta chains are not available for paraffin-embedded tissue), CD3, CD4, CD8, CD20, CD30, CD56, TIA-1, and granzyme B, as well as in situ hybridization for EBV. One should bear in mind that subcutaneous panniculitis-like T-cell lymphoma should be differentiated not only from benign panniculitis, but also from more aggressive lymphomas that may present with identical morphologic features. An antibody useful in differentiating subcutaneous panniculitis-like T-cell lymphoma from benign panniculitis is MIB-1/Ki67: in subcutaneous panniculitis-like T-cell lymphoma the cells show an increased proliferation, and it is often possible to highlight the
so-called “rimming” of adipocytes by proliferating lymphocytes, whereas in benign panniculitis the proliferation is less marked, and lymphocytes around adipocytes are mostly negative for MIB-1. In this context, it should be reminded that “rimming” of adipocytes by neoplastic lymphocytes is not pathognomonic of subcutaneous panniculitis-like T-cell lymphoma, as it can be observed in any lymphoma involving the subcutaneous tissue, even in B-cell lymphomas

One single CGH study of 9 patients demonstrated aberration of the NAV3 gene and many copy number changes of several chromosomes, especially in the subtelomeric chromosomal regions. However, these CGH results have to be interpreted with caution, as the aberrations have not been verified by another method neither in this study nor by another group. One of the main difficulties in the genetic analyses of subcutaneous panniculitis-like T-cell lymphoma is represented by the presence of large areas of necrosis and degenerative changes in many biopsies, and the comparatively small number of neoplastic cells available for molecular analyses.

Primary Cutaneous Marginal Zone Lymphoma

This is one of two lymphoma types that changed terminology between the WHO-EORTC 2005 and the WHO 2008 classifications. In the new WHO classification, cutaneous cases have been lumped together with other extranodal marginal zone lymphomas of the mucosa-associated lymphoid tissue (MALT lymphomas). We believe that cutaneous cases show enough peculiarities to warrant separate classification, but one should acknowledge that many similarities among these extranodal low-grade B-cell lymphomas exist, especially including the link of a proportion of cases to different infectious organisms depending on the organ of origin (i.e., Helicobacter pylori in the stomach, Chlamydia psittaci in the ocular adnexa, and Borrelia burgdorferi in the skin). The clinical diagnosis is very difficult, as lesions present often as inconspicuous, small erythematous nodules on the trunk or upper extremities. Histology shows a population of neoplastic marginal zone cells, lymphoplasmacytoid cells, and plasma cells, usually admixed with a predominant population of reactive lymphocytes and histiocytes. The three neoplastic cell types may be mixed together, or any of the three may be the predominant neoplastic component. Diagnosis of primary cutaneous marginal zone lymphoma relies on typical clinicopathologic features together with the demonstration of monoclonal expression of immunoglobulin light chains (either kappa or lambda). The latter can be easily demonstrated in paraffin embedded tissues by immunohistology or in situ hybridization (fig. 7), and is more sensitive than PCR analysis of the immunoglobulin gene rearrangement (probably due to somatic hypermutations and to the small number of neoplastic cells).

The affinity maturation of the humoral immune response is accomplished by somatic hypermutation, which introduces point mutations in the variable region of immunoglobulin genes of germinal centre B cells. An aberrant activity of the somatic hypermutation process affects...
about 70% of cases of primary cutaneous marginal zone lymphoma and induces mutations in regulatory and coding sequences of multiple genes, including the proto-oncogenes PIM1, PAX5, RhoH/TTF, and MYC. Inactivation of the tumor suppressor genes CDKN2A and DAPK by hypermethylation has been described in about half of cases of primary cutaneous marginal zone lymphoma. Chromosomal translocations that frequently occur in non-cutaneous marginal zone lymphoma of MALT are uncommon in primary cutaneous marginal zone lymphoma. The API2/MALT1 translocation was reported only in one study in about 7% of cases, but was never found in several other studies. The IGH/MALT1 translocation was identified in about 15% of cases in two studies, but not in two other studies. A translocation involving FOXP1 and IGH has been reported in 2 of 20 cases of primary cutaneous marginal zone lymphoma. The translocation BCL10/IGH was never found, and gains of chromosomes 3 and 18 were also infrequently found. Thus, these results suggest that primary cutaneous marginal zone lymphoma and extracutaneous marginal zone lymphoma of MALT have different pathogenetic pathways, supporting the concept that primary cutaneous marginal zone lymphoma should be classified separately from other MALT-lymphomas, just as other types of cutaneous B-cell lymphomas.

Primary Cutaneous Follicle Centre Lymphoma

Together with primary cutaneous marginal zone lymphoma this is the most frequent type of cutaneous B-cell lymphoma, characterized by an excellent prognosis (5-year survival > 95%). Two distinct clinical presentations are typical: one characterized by clustered tumors on the scalp, the second by tumors on the back surrounded by large areas of erythematous papules and macules, often involving
the entire back (this last variant is known also as “Crosti’s lymphoma”). Diagnosis relies on clinical presentation, histologic pattern (which can be purely follicular, mixed follicular and diffuse, or only diffuse, the latter resembling a diffuse large B-cell lymphoma), and demonstration of B lymphocytes with differentiation toward germinal center cells within the follicles and outside of them (CD20+, Bcl-6+, CD10+/−). Cutaneous follicle center lymphoma has been one of the first “organ-specific” lymphomas recognized by hematologists and hematopathologists: only a few years ago the concept of a “primary cutaneous” follicle center lymphoma different from the nodal type was denied by most hematopathologists, and lack of t(14;18) and of Bcl-2 expression were considered inconsistent with the diagnosis of a follicular lymphoma. Today, it is well accepted that cutaneous cases are morphologically identical to nodal ones, but different on the genetic pathway. In addition and of great diagnostic importance, in contrast to what happens in the lymph nodes, the diffuse type of cutaneous follicle center lymphoma is not considered as a diffuse large B-cell lymphoma, as clinical presentation and outcome do not differ from the follicular and mixed types. The germinal centre cell origin of all morphologic types of cutaneous follicle center lymphoma is supported by clonally rearranged immunoglobulin genes and somatic hypermutation of their variable regions. The same monoclonal B-cell population is detected in different lymph follicles as well as in interfollicular areas, confirming that neoplastic cells are actively migrating between follicular and interfollicular areas. A gene expression profile of germinal centre B-cells and an aberrant activity of the somatic hypermutation process, which induces point mutations in the BCL6, MYC, RhoH/TTF, and PAX5 genes in about half of cases, provides additional evidence for a germinal center origin.

It should be reminded that staging investigations must be carried out in all cases of follicle center lymphoma arising in the skin, as clinicopathologic features of primary and secondary cases may be indistinguishable.

The incidence of the translocation (14;18) that involves the BCL2 and IGH genes in cutaneous follicle center lymphoma is controversially discussed. Although this translocation is a hallmark of systemic follicular lymphomas, most studies did not find BCL2 rearrangements in cases arising primary in the skin. Only few studies reported the presence of this translocation in up to 40% of cases. For practical purposes, the detection of BCL2 rearrangements and/or expression of Bcl-2 protein by follicular cells should always raise suspicion of a nodal follicular lymphoma with secondary skin involvement.

Array-based CGH studies in combination with interphase FISH analysis revealed high level DNA amplifications of chromosome region 2p16 (containing the C-REL and BCL11A genes), and loss of chromosome region 14q32 (containing the IGH gene). These aberrations are not found in primary cutaneous diffuse large B-cell lymphoma, leg type. Inactivation of the CDKN2A tumor suppressor either by deletion or by promoter hypermethylation is rarely found in cutaneous follicle center lymphoma. In general, molecular results clearly shows that the diffuse variant of cutaneous follicle center lymphoma is different from primary cutaneous diffuse large B-cell lymphoma, leg type. These results have great practical implications as at extracutaneous sites diffuse follicular lymphomas are considered and treated as diffuse large B-cell lymphomas, whereas in the skin all morphologic variants of cutaneous follicle center lymphoma are treated similarly in a non-aggressive fashion.
Primary Cutaneous Diffuse Large B-Cell Lymphoma, Leg Type

Thanks to the work of the EORTC Cutaneous Lymphoma Project Group, the concept of a “leg-type” cutaneous diffuse large B-cell lymphoma is now widely accepted, and the entity is included as such in the WHO 2008 classification. Indeed, about 80% of the cases of this lymphoma arise on one or both legs, thus justifying the terminology adopted. The diagnosis relies purely on histopathologic and phenotypic features, characterized by the presence of diffuse sheets of large round cells (immunoblasts, centroblasts) that show a typical CD20+\textsuperscript{+}, MUM-1+\textsuperscript{+}, Bcl-2+\textsuperscript{+}, FOX-P1+\textsuperscript{+} phenotype contrasting with the CD20+\textsuperscript{+}, MUM-1-, Bcl-2-, FOX-P1- phenotype of the diffuse variant of pcFCL (fig. 9)\textsuperscript{56}.

On a genetic level many similarities exist between primary cutaneous diffuse large B-cell lymphoma, leg-type, leg type and diffuse large B-cell lymphomas arising at other sites. The post germinal center origin of primary cutaneous diffuse large B-cell lymphoma, leg-type, is confirmed by clonally rearranged immunoglobulin genes and somatic hypermutation of their variable regions. A gene expression profile of activated peripheral B-cells and point mutations in the \textit{BCL6}, \textit{MYC}, \textit{RhoH/TTF}, and \textit{PAX5} genes, induced by an aberrant activity of the somatic hypermutation process, provides further evidence for a postgerminal center origin of this lymphoma\textsuperscript{45,46}.

Using array-based CGH and FISH analyses, deletion of a small region on chromosome 9p21 (including the \textit{CDKN2A} and \textit{CDKN2B} genes) was detected in 67% of cases of primary cutaneous diffuse large B-cell lymphoma, leg-type\textsuperscript{54}. More important, inactivation of \textit{CDKN2A}, either by deletion or promoter hypermethylation, was found to be an important prognostic parameter predicting a 5-year disease-specific survival rate of around 40%, as compared with 70% in cases without deletion\textsuperscript{57}. Although these deletions usually involve larger areas of several kilobase pairs, smaller deletions may not be detected by standard FISH analysis\textsuperscript{58}. High-level DNA amplifications of 18q21, containing the \textit{BCL2} and \textit{MALTI} genes, were detected in 67% of cases of primary cutaneous diffuse large B-cell lymphoma, leg-type\textsuperscript{54}. Copy number changes were identified in 80–100%, the most common findings being gains in chromosomes 1, 2, 3, 7, 12, and 18q and losses in 6q, 13, and 17\textsuperscript{23,59,60}. Interphase FISH analysis demonstrated translocations involving \textit{MYC}, \textit{BCL2}, and \textit{BCL6}\textsuperscript{69,60}. Chromosomal amplification of \textit{BCL2} and the translocation \textit{IGH/BCL2}, which is also found at low incidence in primary cutaneous diffuse large B-cell lymphoma, leg-type, may explain the strong Bcl-2 protein expression observed in this lymphoma\textsuperscript{59}.

Molecular data in primary cutaneous diffuse large B-cell lymphoma, leg-type may soon find translation into clinical practice, as the reported inactivation of \textit{CDKN2A} is characterized by a strong prognostic implication.

Blastic Plasmacytoid Dendritic Cell Neoplasm

This is probably the hematologic neoplasm that has changed name more often in the last years (formerly was known as blastic NK cell lymphoma or CD4+\textsuperscript{+}/CD56+ hematodermic neoplasm among many other terms). Although the skin is often the primary site of onset (in many cases with negative staging at presentation), it is now accepted that blastic plasmacytoid dendritic cell neoplasm represents a form of aleukemic leukemia cutis with many similarities to myelogenous leukemia. The diagnosis can be suspected clinically by the presence of one or, more commonly, several hemorrhagic (bruise-like) tumors. Complete phenotypic investigations are mandatory for a
diagnosis (CD4+, CD56+, CD123+, BDCA2+ phenotype with negativity of T and B cell markers and variable positivity of many other markers such as TdT, CD68 and IRF8 among others). Aberrant phenotypic features can be observed (negativity for one or more among CD4, CD56 and CD123), thus presenting difficulties in the precise diagnosis and classification\textsuperscript{61}. In some cases unequivocal differentiation from myelogenous leukemia is not possible, and in some patients blastic plasmacytoid dendritic cell neoplasm has occurred on the background of a myelodysplastic syndrome, underlying the relationship between these entities.

Figure 9. Cutaneous diffuse large B-cell lymphoma, leg-type. A. Solitary tumour on the lower leg of an 85-year-old man. B. Predominance of large lymphocytes with round nuclei positive for Bcl-2 (C), MUM-1 (D), and FOX-P1 (E).
Molecular analyses of blastic plasmacytoid dendritic cell neoplasm revealed commonly complex karyotypes with large chromosomal aberrations. Losses on chromosomes 9, 12, and 13 are detected in more than 50% of cases (fig. 10). In about 65% of patients a deletion at chromosome region 12p13, which contains the CDKN1B gene, can be observed (fig. 10). CDKN1B belongs to an atypical class of tumour suppressor genes that do not conform to the Knudson’s “2-hit” model. At high expression levels, CDKN1B causes cell-cycle arrest and suppresses tumor growth, but at low expression levels acts as an oncogene. Although deletions or mutations of CDKN1B are rare in other human cancers, a reduced expression is common in many neoplasms and is highly correlated with poor prognosis. Additionally, mono- and biallelic deletions on chromosome 9p21, including the CDKN2A and CDKN2B gene, and losses of chromosome 13, harbouring the RB1 gene, are detected in about 50% of patients. All these frequently deleted genes are cell cycle regulators, indicating that alterations of the cell cycle are crucial in the oncogenesis of this neoplasm.

**Other Cutaneous Lymphomas**

Many other lymphomas may arise primary in the skin, such as intravascular lymphoma (both of B- or NK/T-cell phenotype) or adult T-cell lymphoma/leukemia for example. Advances in the diagnosis of these cases are mainly represented by better defined phenotypic features, as genetic investigations are not yet in a sufficiently advanced stage to be applied to routine diagnosis. Some entities, such as small-medium pleomorphic T-cell lymphoma, are not yet well defined and are listed only as provisional entities in the WHO 2008 classification. One important group is represented by the aggressive cytotoxic NK/T-cell lymphomas. These are rare diseases which in the past were considered as aggressive variants of mycosis fungoides, but that today are classified separately. The best defined among them is extranodal NK/T-cell lymphoma, nasal-type, which may arise primary in the skin and is associated with EBV infection. The other two entities, namely, cutaneous gamma/delta T-cell lymphoma and cutaneous epidermotropic CD8+ aggressive T-cell lymphoma show many overlapping features with one another and with mycosis fungoides, and an exact classification is sometimes very difficult. Due to their rarity, molecular data on these disorders are very scarce. At present, the diagnosis is based on the combination of clinical presentation, clinical history (absence of history of mycosis fungoides), histopathologic features, and immunophenotype. Another peculiar group of lymphomas arising in the setting of immune dysregulation is of relevance for dermatologists and dermatopathologists. These lymphomas may arise primary in the skin, and represent a heterogenous group of disorders often associated with EBV infection. They are observed either in the setting of infection-related immunosuppression (i.e., due to human immunodeficiency virus infection), or of hereditary syndromes (i.e., congenital immune deficiencies), or of iatrogenic immune suppression (i.e., due to immunosuppressive treatment after organ transplantation). Their exact classification is of great importance, as in many cases they respond to reduction of immune suppression without aggressive treatment. Specific genetic alterations are not yet known, and the diagnosis is based on the clinical setting and on histopathologic and phenotypic features.

**Looking Forward in Cutaneous Lymphomas**

The pace of changes in the diagnosis and understanding of cutaneous lymphomas is impressive. A glance at the classification systems used in the early 90s (updated Kiel classification and later Revised European-American Lymphoma – REAL classification, both devised for systemic
lymphomas only) and a comparison with the clinicopathologic approach used in the WHO 2008 scheme is the best way to realize the incredible changes that have occurred in the last 20 years. On the other hand, dermatologists and dermatopathologists are conversant for a long time with most of the entities that are listed in the WHO 2008 classification. Mycosis fungoides, Sézary syndrome, lymphomatoid papulosis and many other cutaneous lymphomas are well known by the dermatologic world for decades or even centuries. Dermatologists have been the first who recognized the concept of organ-based lymphomas, a concept that has been first strongly resisted by hematologists and hematopathologists, but that now has been fully incorporated within the WHO 2008 classification system.

Diagnostic advances in the last years mainly relied on the application of monoclonal antibodies to identify antigen on neoplastic cells, and on studies of the gene rearrangement pattern of the TCR and IgH genes, resulting in a considerable improvement in diagnosis and especially in classification of controversial entities (such as subcutaneous panniculitis T-cell lymphoma for example). On the other hand, classic morphology is still at the base of the diagnosis of cutaneous lymphomas (an example is represented by intravascular lymphoma, where diagnosis cannot be made without the histologic feature of intravascular location of neoplastic cells; in this lymphoma, phenotypic features are less important, and NK/T- and B-cell cases are still classified and managed as a single entity). In early lesions of mycosis fungoides, clinical diagnosis is often more accurate than histopathologic examination, particularly because biopsies are often performed after application of different treatments that mask typical features of the disease such as epidermotropism. Morphology alone, however, is no longer enough for making precise diagnoses, and dermatologists and dermatopathologists should realize that cutaneous lymphomas may be classified correctly only upon the synthesis of complete clinical information and histopathologic, immunohistochemical, and often molecular features.

We cannot foresee the future (nor can others…), but it is an easy guess that molecular analyses will rapidly bring a vast amount of new information in the field of cutaneous lymphomas, just as in any other field of dermatology and of medicine in general. This does not necessarily means that “conventional” diagnostic techniques will be abandoned: it is more likely that new molecules identified at the genetic level will be testable at the protein level by antibodies, thus broadening the spectrum of possibilities to make more specific and more sensitive diagnoses, and more accurate estimates of prognosis.

Conflict of interests
Authors have no conflict of interests to declare.

References
45. Dijkman R, Tensen C, Buettner M, Niedobitek G, Willemze R, Vermeer M. Primary cutaneous follicle center lymphoma and primary cutaneous large B-cell lymphoma, leg type, are


