CHAPTER 1

Introduction

Primary cutaneous lymphomas represent distinct clinical and histopathologic subtypes of extranodal lymphomas. They can be defined as neoplasms of the immune system, characterized by a proliferation of either T, natural killer (NK), or B lymphocytes, which show a particular tropism for the skin. By definition, primary cutaneous lymphomas show no evidence of extracutaneous manifestations at presentation. Besides malignant lymphomas, the skin may be the primary site of onset of other hematological malignancies such as myeloid leukemia ("aleukemic leukemia cutis") and blastic plasmacytoid dendritic cell neoplasm; although staging investigations may be negative at presentation, these disorders should be better regarded as a secondary cutaneous manifestation of an undiscovered malignant hematological disease, and treated accordingly.

Primary cutaneous lymphomas should be separated from secondary skin manifestations of extracutaneous (usually nodal) lymphomas and leukemias, which represent metastatic disease characterized usually by a worse prognosis, and requiring different treatments. Since the histopathology of primary and secondary cutaneous lymphomas may be similar or identical, in many cases complete staging investigations are needed to establish this distinction (early mycosis fungoides representing the most important, but not the only exception to this rule).

Besides cutaneous lymphomas, many diseases that simulate them either clinically, histopathologically, or both, are a daily source of diagnostic problems (cutaneous pseudolymphomas). Criteria for diagnosis and differential diagnosis of these benign lymphoproliferative conditions are discussed in Chapter 31 of this book.

Finally, besides infiltration by neoplastic lymphocytes, the skin may present with several specific or nonspecific signs and symptoms related to extracutaneous lymphomas, some of which are highly suggestive of specific conditions. A discussion of nonneoplastic cutaneous manifestations of systemic lymphomas and leukemias is provided in Chapter 29.

Classification of cutaneous lymphomas

Regrettably, as in past times, different classifications for lymphomas and leukemias are again in use. A Clinical Advisory Committee (CAC) together with world leading hematopathologists published the International Consensus Classification (ICC) *of Myeloid and Lymphoid Neoplasms* in 2022 [1] (the ICC book has been subsequently published in 2025) [2]. On the other hand, the World Health Organization (WHO), prepared in 2022 the 5th revision of the *Classification of Haematolymphoid Tumours* [3, 4] (the WHO book has been subsequently published in two volumes in 2024) [5]. However, the ICC and WHO schemes differ only in some parts, and there is no major discrepancy for what concerns skin lymphomas; the entities relevant for the skin are listed in Table 1.1. For what concerns cutaneous lymphomas, the ICC and WHO schemes are based on the seminal work made by the European Organization for Research and Treatment of Cancer (EORTC) – Cutaneous Lymphomas Task Force, which in 1997 published the first comprehensive classification of cutaneous lymphomas [6], subsequently revised together with a WHO panel in 2005 and 2018, and updated in 2024 (Table 1.1) [7]. In fact, in contrast to previous editions, in the last edition of the WHO *Classification of Haematolymphoid Tumours* published in 2024, primary cutaneous T-cell lymphomas are listed as a distinct group (most primary cutaneous B-cell lymphomas are referred to as specific entities in the context of other extracutaneous B-cell lymphomas) [3]. Curiously enough, however, Sézary syndrome has not been included in the group of cutaneous T-cell lymphomas in the WHO classification. The recognition of cutaneous lymphomas as a distinct group (after decades of disregard by most hematopathologists) is mainly due to the work done in the past by the Dutch and Austrian groups, particularly by Rein Willemze and Helmut Kerl.

Despite the presence of an accepted frame for classification of primary cutaneous lymphomas, in many publications obsolete terminology such as "cutaneous T-cell lymphoma" is still used. Under this term cases of mycosis fungoides and Sézary syndrome (and sometimes of other T-cell lymphomas arising in the skin as well) are lumped together, thus hindering any meaningful analysis of the published data. In order to compare data, it is paramount that physicians in different countries and centers classify cutaneous lymphomas in a repeatable way.

Skin Lymphoma: The Illustrated Guide, Sixth Edition. Lorenzo Cerroni.

Table 1.1 Comparison of the International Consensus Classification *of Myeloid and Lymphoid Neoplasms* and the 5th edition of the WHO *Classification of Haematolymphoid Tumours* for entities relevant to the skin, and corresponding entities in the 2018 WHO-EORTC Classification of Cutaneous Lymphomas

International consensus classification	WHO 5ed	2018 WHO-EORTC classification of cutaneous Ly.
Mycosis fungoides and variants	Mycosis fungoides and variants	Mycosis fungoides and variants
Folliculotropic mycosis fungoides	*Folliculotropic mycosis fungoides*	*Folliculotropic mycosis fungoides*
Pagetoid reticulosis	*Pagetoid reticulosis*	*Pagetoid reticulosis*
Granulomatous slack skin	*Granulomatous slack skin*	*Granulomatous slack skin*
Sézary syndrome	Sézary syndrome	Sézary syndrome
Adult T-cell leukemia/lymphoma	Adult T-cell leukemia/lymphoma	Adult T-cell leukemia/lymphoma
Cutaneous CD30⁺ lymphoproliferative disorders	Cutaneous CD30⁺ lymphoproliferative disorders	Cutaneous CD30⁺ lymphoproliferative disorders
Cutaneous anaplastic large cell lymphoma	*Cutaneous anaplastic large cell lymphoma*	*Cutaneous anaplastic large cell lymphoma*
Lymphomatoid papulosis	*Lymphomatoid papulosis*	*Lymphomatoid papulosis*
Subcutaneous panniculitis-like T-cell lymphoma	Subcutaneous panniculitis-like T-cell lymphoma	Subcutaneous panniculitis-like T-cell lymphoma
Extranodal NK/T-lymphoma, nasal-type	Extranodal NK/T-lymphoma, nasal-type	Extranodal NK/T-lymphoma, nasal-type
Cutaneous γ/δ T-cell lymphoma	Cutaneous γ/δ T-cell lymphoma	Cutaneous γ/δ T-cell lymphoma
Cutaneous aggressive epidermotropic CD8+ CTCL	Cutaneous aggressive epidermotropic CD8+ CTCL	Cutaneous aggressive epidermotropic CD8+ CTCL *(provisional)*
pCSMPCD4⁺ T-cell lymphoproliferative disorder	pCSMPCD4⁺ T-cell lymphoproliferative disorder	pCSMPCD4⁺ T-cell lymphoproliferative disorder *(provisional)*
Acral CD8⁺ T-cell lymphoproliferative disorder	Acral CD8⁺ T-cell lymphoproliferative disorder	Acral CD8⁺ T-cell lymphoma *(provisional)*
EBV⁺ T/NK-cell lymphoproliferative disorders of childhood	EBV⁺ T/NK-cell LPs and lymphomas of childhood	Chronic active EBV infection
Peripheral T-cell lymphoma, NOS	Cutaneous peripheral T-cell lymphoma, NOS	Cutaneous peripheral T-cell lymphoma, NOS
Cutaneous marginal zone lymphoproliferative disorder	Cutaneous marginal zone lymphoma	Cutaneous marginal zone lymphoma
Cutaneous follicle center lymphoma	Cutaneous follicle center lymphoma	Cutaneous follicle center lymphoma
Cutaneous diffuse large B-cell lymphoma, leg-type	Cutaneous diffuse large B-cell lymphoma, leg-type	Cutaneous diffuse large B-cell lymphoma, leg-type
Intravascular large B-cell lymphoma	Intravascular large B-cell lymphoma	Intravascular large B-cell lymphoma
EBV⁺ mucocutaneous ulcer	EBV⁺ mucocutaneous ulcer	EBV⁺ mucocutaneous ulcer *(provisional)*

NK: natural killer; CTCL: cutaneous T-cell lymphoma; pCSMPCD4⁺: primary cutaneous small/medium pleomorphic CD4-positive; NOS; not otherwise specified; LPs: lymphoid proliferations.

Examination of patients

Primary cutaneous lymphomas represent a heterogeneous group of diseases with different clinicopathologic presentations and prognostic features. In order to classify patients correctly, it is crucial that a complete clinical history is obtained and integrated with histopathologic, immunophenotypical, and molecular data. To take but one example, some lesions of lymphomatoid papulosis show histopathologic features that may be indistinguishable from those observed in mycosis fungoides, anaplastic large cell lymphoma, or cutaneous CD8⁺ aggressive epidermotropic cytotoxic T-cell lymphoma, and differentiation can only be achieved by correlation with the clinical picture.

Staging investigations

As a general rule, complete staging investigations at presentation include physical examination, laboratory investigations, ultrasound of lymph nodes and visceral organs, computed tomography (CT) scans and/or positron emission tomography (PET), and bone marrow biopsy. In most centers, PET has replaced CT as the first choice for radiological staging. Patients with several types of low-grade cutaneous lymphoma (e.g., mycosis fungoides, lymphomatoid papulosis, and subcutaneous panniculitis-like T-cell lymphoma among others) do not require extensive investigations. Patients with cutaneous CD4⁺ small–medium T-cell lymphoproliferative disorder, too, do not require staging investigations. The necessity of staging investigations in patients with primary cutaneous marginal zone lymphoproliferative disorder is also questionable [8], and many centers do not suggest to perform it in otherwise asymptomatic patients.

A staging classification system for mycosis fungoides, Sézary syndrome, and other cutaneous T- and B-cell lymphomas was proposed by a joint working group of the International Society of Cutaneous Lymphoma (ISCL) and the EORTC Cutaneous Lymphoma Task Force [9]. This system has been subsequently slightly modified in conjunction with the United States Cutaneous Lymphoma Consortium (USCLC) (Tables 1.2 and 1.3) [11, 12].

Surgical techniques

In general, when dealing with cutaneous lymphomas shave biopsies must be avoided (Fig. 1.1). A possible exception may be represented by early lesions of mycosis fungoides, in which a

Table 1.2 Staging of mycosis fungoides and Sézary syndrome according to the ISCL–EORTC–USCLC

Skin					
T_0	Absence of clinically suspicious lesions				
T_1	Limited patches*, papules, and/or plaques† covering <10% of the skin surface. May be further stratified into T_{1a} (patches only) versus T_{1b} (plaques ± patches)				
T_2	Patches, papules, or plaques covering >10% of the skin surface. May be further stratified into T_{2a} (patches only) versus T_{2b} (plaques ± patches)				
T_3	One or more tumors‡ (≥1 cm diameter)				
T_4	Confluence of erythema covering ≥80% body surface area				
Lymph nodes					
N_0	No clinically abnormal peripheral lymph nodes§; biopsy not required				
N_1	Clinically abnormal peripheral lymph nodes; histopathology Dutch grade 1 or NCI LN0-2				
	N_{1a} Clone negative or equivocal				
	N_{1b} Clone positive and identical to skin				
N_2	Clinically abnormal peripheral lymph nodes; histopathology Dutch grade 2 or NCI LN3				
	N_{2a} Clone negative or equivocal				
	N_{2b} Clone positive and identical to skin				
N_3	Clinically abnormal peripheral lymph nodes; histopathology Dutch grades 3–4 or NCI LN4				
	N_{3a} Clone negative or equivocal				
	N_{3b} Clone positive and identical to skin				
N_x	Clinically abnormal peripheral lymph nodes; no histologic confirmation				
Visceral					
M_0	No visceral organ involvement				
M_{1a}	Bone marrow only involvement				
	Clone negative or equivocal				
	Clone positive and identical to skin				
M_{1b}	Nonbone marrow visceral involvement				
	Clone negative or equivocal				
	Clone positive and identical to skin				
M_x	Visceral involvement is neither confirmed nor refuted by available pathologic or imaging assessment				
Blood&					
B_0	Absence of significant blood involvement: ≤250/μL of $CD4^+/CD26^-$ or $CD4^+/CD7^-$cells				
	B_{0a} Clone negative or equivocal				
	B_{0b} Clone positive and identical to skin				
B_1	Low blood tumor burden: does not meet the criteria for B_0 or B_2				
	B_{1a} Clone negative or equivocal				
	B_{1b} Clone positive and identical to skin				
B_2	High blood tumor burden: ≥1000/μL of $CD4^+/CD26^-$ or $CD4^+/CD7^-$cells or other aberrant population of lymphocytes identified by flow cytometry				
	B_{2a} Clone negative or equivocal				
	B_{2b} Clone positive and identical to skin				
B_X	Unable to quantify blood involvement according to agreed upon guidelines				
	B_{Xa} Clone negative or equivocal				
	B_{Xb} Clone positive and identical to skin				
Stage(z)					
IA	$T_1N_0M_0B_{0,1}$	IB	$T_2N_0M_0B_{0,1}$		
IIA	$T_{1,2}N_{1,2}M_0B_{0,1}$	IIB	$T_3N_{0-2}M_0B_{0,1}$		
IIIA	$T_4N_{0-2}M_0B_0$	IIIB	$T_4N_{0-2}M_0B_1$		
IVA1	$T_{1-4}N_{0-2}M_0B_2$	IVA2	$T_{1-4}N_3M_0B_{0-2}$	IVB	$T_{1-4}N_{0-3}M_{1A,B}B_{0-2}$

* For skin, a patch indicates any size skin lesion without significant elevation or induration. The presence/absence of hypo- or hyperpigmentation, scale, crusting, and/or poikiloderma should be noted.

† For skin, plaque indicates any size skin lesion that is elevated or indurated. The presence or absence of scale, crusting, and/or poikiloderma should be noted. Histologic features such as folliculotropism or large cell transformation (>25% large cells), $CD30^+$ or $CD30^-$, and clinical features such as ulceration are important to document.

‡ For skin, the tumor indicates at least one ≥1 cm diameter solid or nodular lesion with evidence of depth and/or vertical growth. Note a total number of lesions, total volume of lesions, largest size lesion, and region of body involved. Also note if histologic evidence of large cell transformation has occurred. Phenotyping for CD30 is encouraged.

§ For node, Abnormal lymph nodes are those >1.5 cm longest diameter according to the Lugano classification [10] and confirmed by imaging. The pathological findings of a representative abnormal lymph node may apply to all abnormal lymph nodes.

¶ For viscera, the spleen and liver may be diagnosed by imaging criteria.

& For blood, it is expected that patients with high blood tumor burden (B_2) will have a clone in the blood that is identical to that in the skin. Nonidentical T-cell clones are often detected in peripheral blood with increasing age and are of unknown clinical significance. Patients with lymphopenia (defined as <1000 absolute lymphocytes) may potentially have an underestimation of aberrant lymphocyte burden if assessed only by the absolute number and not also by the percentage of immunophenotypically abnormal lymphocytes.

(z) Folliculotropism is a histologic feature that can occur irrespective of stage. Histologic evidence of FMF is associated with a higher risk of disease progression. In selected cases or inadequate response, consider primary treatment for stage IIB (tumor stage disease). Adapted from Olsen *et al*. [11].

Table 1.3 TNM classification system for cutaneous lymphomas other than mycosis fungoides and Sézary syndrome

Classification	Description
T_1	Solitary skin involvement T_{1a}: Solitary lesion <5 cm in diameter T_{1b}: Solitary lesion ≥5 cm in diameter
T_2	Regional involvement of skin: multiple lesions limited to 1 body region or 2 contiguous body regions T_{2a}: All disease encompassing a <15-cm-diameter circular area T_{2b}: All disease encompassing a ≥15 to <30-cm-diameter circular area T_{2c}: All disease encompassing a ≥30-cm-diameter circular area
T_3	Generalized skin involvement T_{3a}: Multiple lesions involving 2 noncontiguous body regions T_{3b}: Multiple lesions involving ≥3 body regions
N_0	No clinical or pathologic involvement of lymph nodes
N_1	Involvement of 1 peripheral lymph node region that drains an area of current or previous skin involvement; biopsy positive for lymphoma
N_2	Involvement of ≥2 peripheral lymph node regions or involvement of any lymph node region that does not drain an area of current or previous skin involvement; biopsy positive for lymphoma
N_3	Involvement of central lymph nodes; biopsy positive for lymphoma
N_X	Clinically abnormal peripheral or central LN but no pathologic determination.
M_0	No visceral involvement
M_1	Visceral involvement
M_X	Visceral involvement is neither confirmed nor refuted by available pathologic or imaging assessment

Adapted from Olsen *et al*. [11].

broad surface of the biopsy may be more useful than a small punch biopsy – provided, of course, that the shave biopsy is deep enough to include the superficial part of the reticular dermis. Punch biopsies may provide sufficient diagnostic information, particularly in tumors with homogeneous populations of cells, but may be too small for phenotypic and genetic analyses, if needed. Particularly in biopsy of suspect early mycosis fungoides, it is a good rule to perform more biopsies on different lesions, in order to get as much information as possible.

Surgical artifacts

Surgical specimens should be carefully removed, paying particular attention not to crush the tissue and not to put surgical specimens on a gauze. Unfortunately, many dermatological surgeons are unaware of the deleterious effects of gauzes on surgical specimens, particularly in biopsies of small dimensions, and even more regrettably, many dermatology textbooks describe the use of gauzes for placing surgical specimens as a standard procedure. Upon contact with a gauze, otherwise adequate biopsies show variable alterations of cell morphology, similar to what can be seen in fixation artifacts (Fig. 1.2). Drying artifacts may render a precise diagnosis impossible even in a large, seemingly well-done punch biopsy (Fig. 1.3). Some cell types get these artifacts in a matter of a few moments (e.g., blastoid cells of large cell lymphomas/leukemias), whereas other are more resistant. The same deleterious effect can be observed in other cutaneous tumors (e.g., Merkel cell carcinoma). Immunohistochemical analyses may still offer some information on specimens with drying artifacts, but as a morphologic-phenotypic correlation is no longer possible, the histologic report should mention that the evaluation of immunohistology is seriously hindered by the artifacts. Other surgical and technical artifacts may reduce, sometimes dramatically, the ability of a dermatopathologist to render a precise diagnosis, such as crushing of a specimen, reduced fixation (due often to the insufficient amount of formalin used to send the specimen to the processing laboratory), heat and freezing artifacts (evident in hot summers and cold winters, particularly in specimens that are processed at sites distant from the surgical theatre), and cauterization artifacts (due to the use of cauterizing surgical blades – so-called "harmonic scalpels"). It is imperative that dermatological surgeons submitting specimens with such artifacts are made aware of the problem, in order to avoid in future unnecessary repetition of the biopsies.

Histopathology, immunophenotype, and molecular genetics

Histopathology

Sections should be cut with a maximum thickness of 4 μm (we use 3.5 μm) and subsequently stained with hematoxylin and eosin (H&E). Stainings with periodic acid–Schiff (PAS) and Giemsa are not performed routinely on skin specimens but may be helpful in specific settings. High-quality sections are necessary for a correct diagnosis.

Morphologic examination of a biopsy specimen should assess the following criteria:

1. Architecture of the infiltrate (e.g., superficial, superficial and deep, subcutaneous, etc.)
2. Involvement of particular structures (e.g., epidermotropism, pilotropism, etc.)
3. Cell composition (e.g., monomorphous infiltrate, mixed cell infiltrate, etc.)
4. Cell morphology
5. Other specific clues and criteria (e.g., deposition of mucin within the hair follicles, angiocentricity/angiodestruction, etc.).

Much information can be gathered at low power by examination of the pattern of growth, and basic morphologic assessment is also useful for the selection of appropriate panels of antibodies necessary for phenotypic analyses, and of other ancillary techniques useful in the study of the biopsy specimen.

Immunophenotype

Staining techniques and automated immunostainers have allowed the standardization of phenotypic studies on formalin fixed, paraffin-embedded (FFPE) tissue sections. A list of antibodies

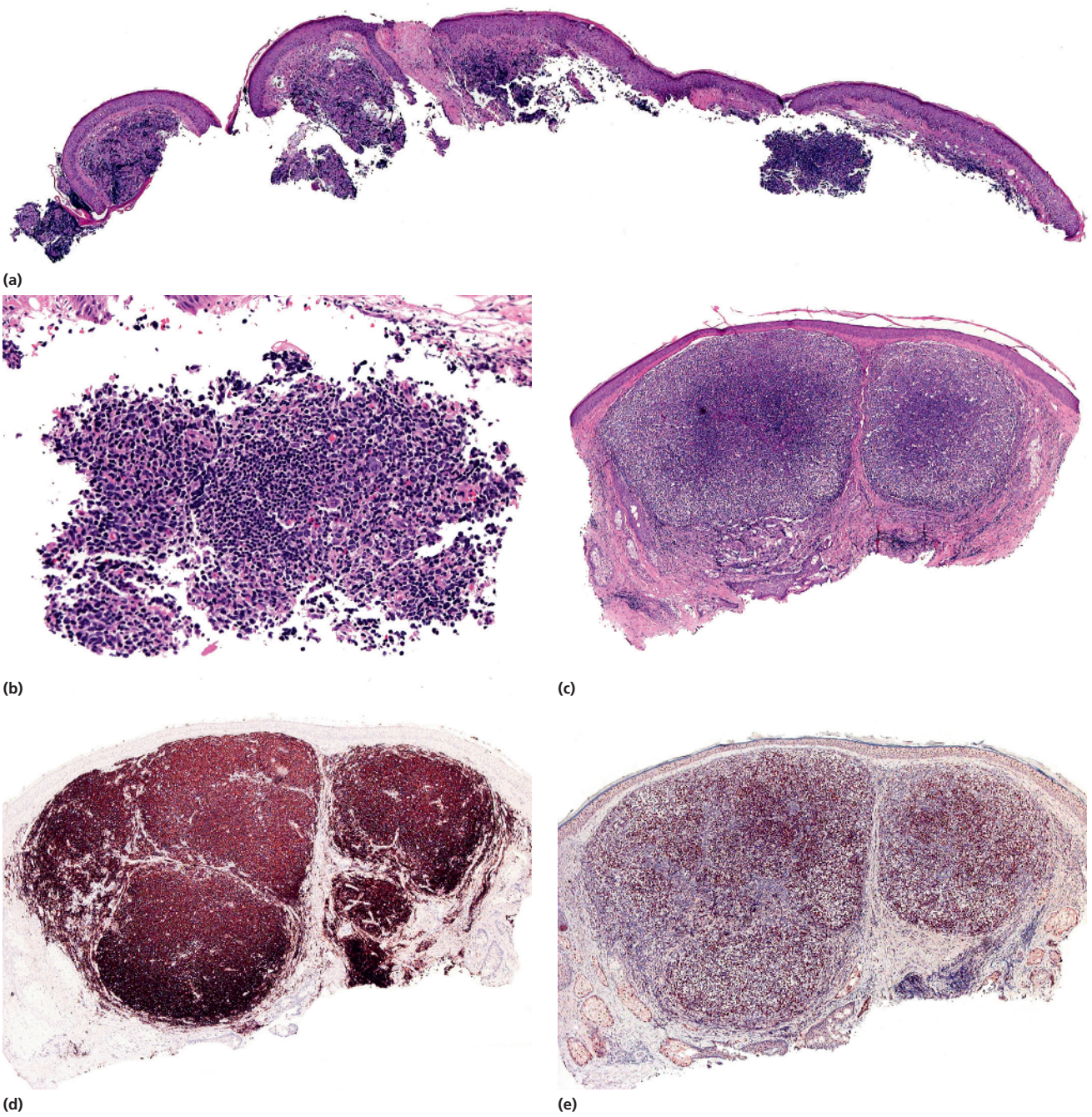

Figure 1.1 Surgical artifact due to a superficial shave biopsy. (a) Superficial shave biopsy taken from the nose under the clinical diagnosis of "r/o basal cell carcinoma" revealed a flat epidermis and fragments of lymphoid infiltrates. (b) Some of the cells within the infiltrate had large nuclei and a new, deeper biopsy was advised. (c) An adequate, new biopsy showed nodular lymphoid infiltrates with a biphasic pattern characterized by mid-sized and large cells arranged at the periphery of the nodules, suggestive of follicle center lymphoma. (d) Positivity for CD20. (e) Bcl-6 confirmed the diagnosis. A high level of suspicion should be exerted when atypical lymphoid infiltrates are only partially sampled. In this context, a punch biopsy is a better type of partial sampling of a cutaneous lymphoid infiltrate than a shave biopsy.

reactive with lymphocyte subsets and accessory cells in FFPE tissue sections is provided in Table 1.4. It should be emphasized that immunohistochemical stainings are not necessary in each and every case of cutaneous lymphoma/pseudolymphoma. In early lesions of mycosis fungoides, for example, I seldom use immunohistology as a routine investigation: in fact, correlation with the clinical picture is faster, cheaper, and gives better information in order to establish the diagnosis. Sometimes, however, staining for pan-T-cell markers may be useful in better displaying the number and distribution of intraepithelial lymphocytes.

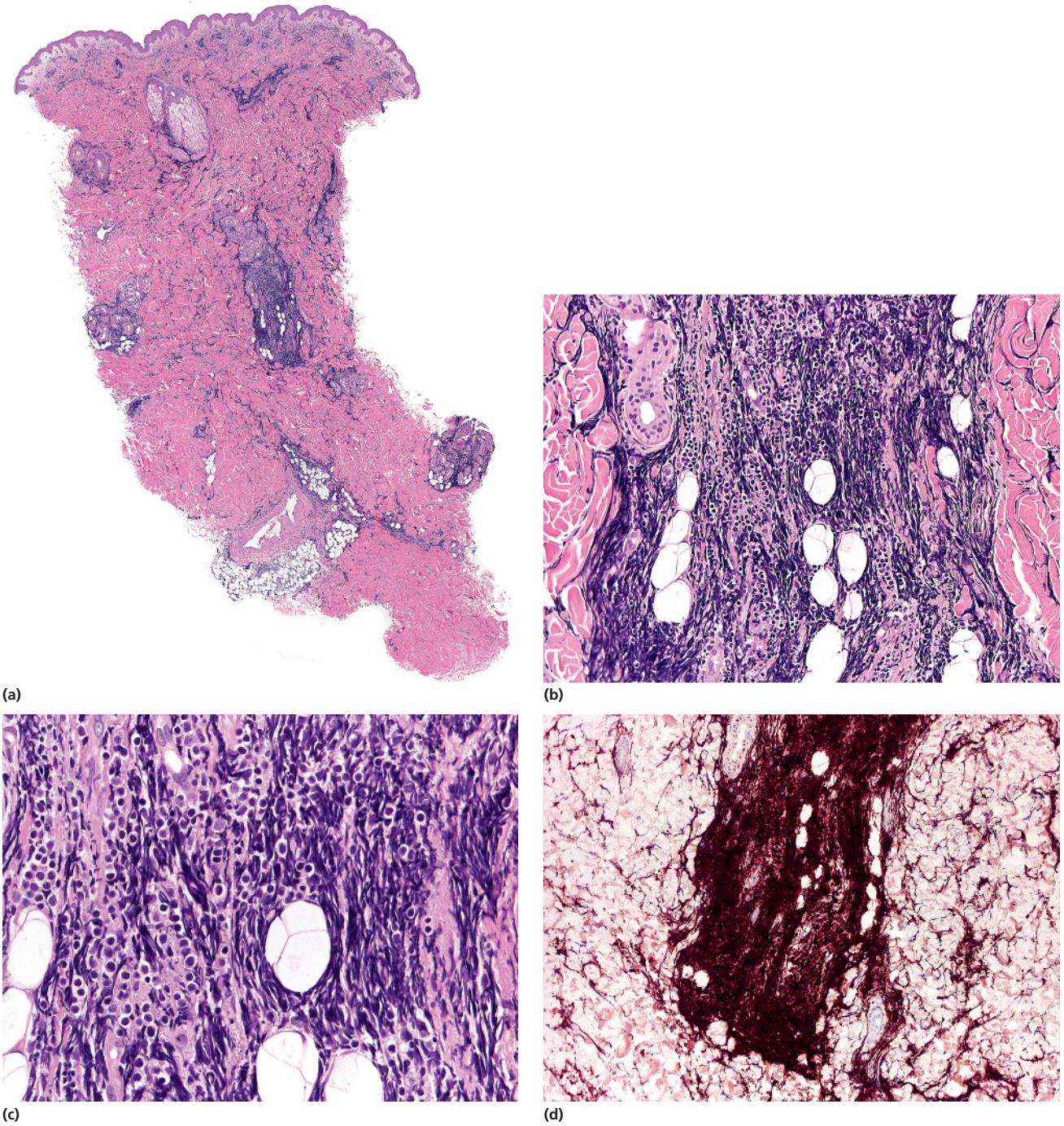

Figure 1.2 Surgical artifact due to placing the biopsy on a gauze (drying artifacts). (a) A 4 mm punch biopsy originally well taken and deep enough (b) shows at high power severe drying artifacts that affect most of the neoplastic cells within the infiltrate; (c) some of the evaluable cells show a mid-sized blastoid appearance. (d) Staining for TdT shows a possible positivity of the cells, but the exact interpretation is hindered by the artifacts. The diagnosis of T lymphoblastic lymphoma was subsequently confirmed by a new biopsy.

Although phenotypic investigations provide crucial information for the diagnosis and classification of cutaneous lymphomas, it should be remembered that malignant cells are characterized by a "plasticity" that may transcend the relatively rigid schemes of our classifications. Besides aberrant expressions of phenotypic markers ("lineage infidelity"), cases with so-called "transdifferentiation," that is, the evolution of a tumor into a clonally related neoplasm of a different cell line has been

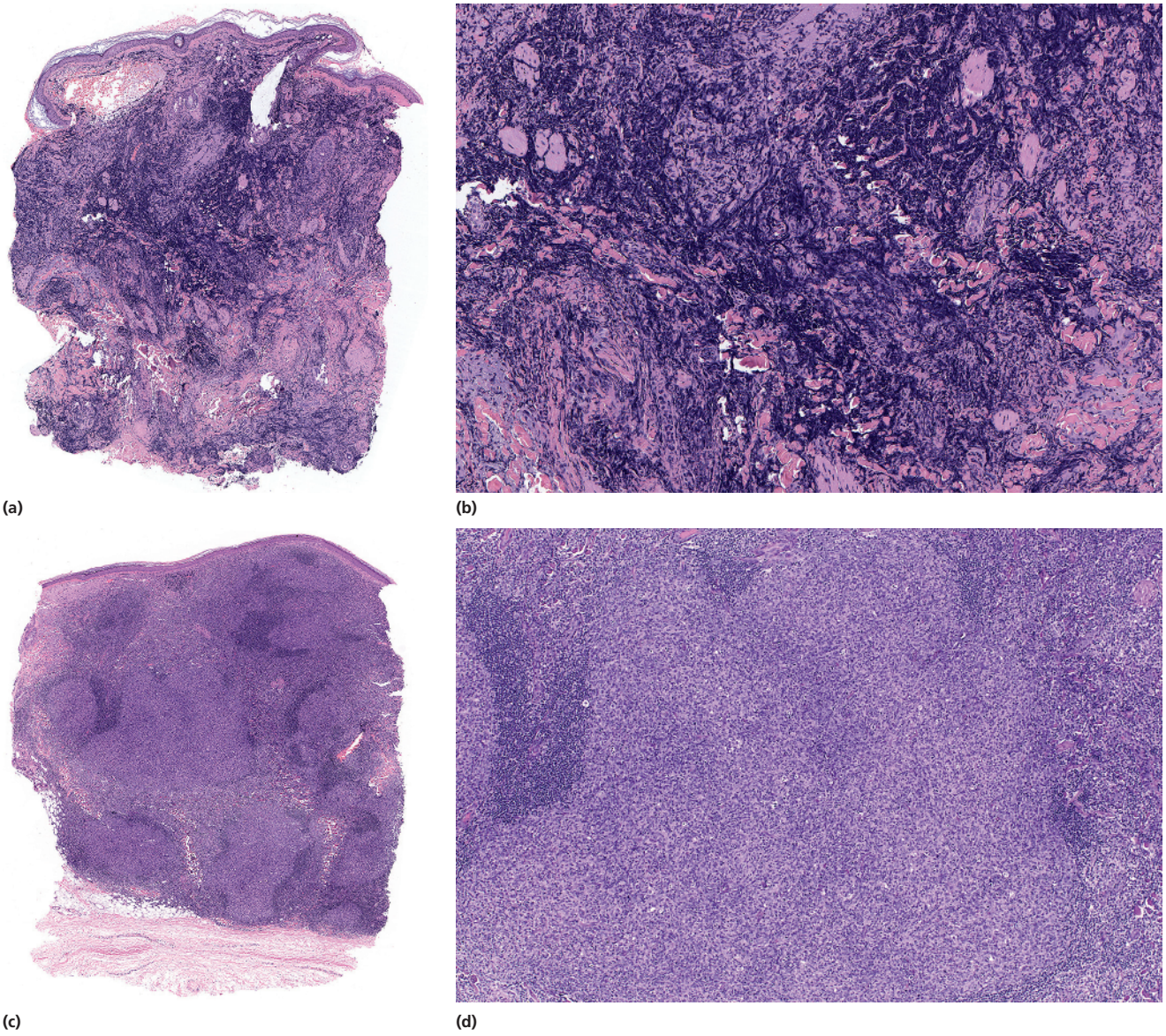

Figure 1.3 Surgical artifact due to placing the biopsy on a gauze (drying artifacts). (a) A 5 mm punch biopsy originally well taken (b) shows severe drying artifacts that affect most of the neoplastic cells within the infiltrate; (c) a repeat biopsy without artifacts shows the same architectural pattern of the infiltrate, (d) and allows to clearly recognize the histopathological features of cutaneous follicle center lymphoma.

described [13]. Although transdifferentiation was thought to be peculiar to precursor lymphomas/leukemias, it has been observed also in mature B-cell neoplasms that have evolved into clonally related dendritic or histiocytic tumors [14]. Overlapping myeloid and lymphoid features can be observed in chronic myelogenous leukemia, in which blast crisis in 10% of the cases reveals a B- or, more rarely, a T-cell phenotype. In some cases, molecular data have provided a rational explanation for the association of different diseases, such as the presence of *TET2* mutations in both angioimmunoblastic T-cell lymphoma and chronic myelomonocytic leukemia, explaining the observation of patients presenting with both diseases. The concept of transdifferentiation expands the traditional model of hematopoiesis based on the unidirectional maturation of hematopoietic precursors into lineage-committed cells. Even normal lymphocytes, particularly B-cells, under appropriate environmental conditions may transdifferentiate into macrophages or other hematopoietic cell types [15].

Gene rearrangement studies

Analysis of the T-cell receptor (TCR) and immunoglobulin (Ig) genes provides useful information for the study of

Table 1.4 Panel of antibodies for immunohistologic analysis of cutaneous lymphomas and pseudolymphomas on routinely fixed, paraffin-embedded sections of tissue

Antigen/antibody	Main immunostaining in cutaneous lymphomas/pseudolymphomas and/or specificity
CD1a	Positive in reactive and neoplastic Langerhans cells. Positivity also in most precursor T-cell lymphomas/leukemias. Useful also in the differential diagnosis of dendritic cell proliferations in patients with chronic myeloid neoplasms.
CD2	Pan T-cell marker. Loss of expression is never found in reactive T-cell infiltrates. Positive also in systemic mastocytosis and in a subset of myeloid neoplasms.
CD2AP	Plasmacytoid dendritic cells; Positive in blastic plasmacytoid dendritic cell neoplasm.
CD3	Pan T-cell marker. Loss of expression is never found in reactive T-cell infiltrates.
CD3ε	T-cells (epsilon chain of CD3). Positive in T cells and also in some NK-cell neoplasms.
CD4	Positive in T-helper cells and related T-cell lymphomas. Commonly positive also in myeloid neoplasms and in blastic plasmacytoid dendritic cell neoplasm.
CD5	Pan T-cell marker. Loss of expression is never found in reactive T-cell infiltrates. Also positive in B lymphocytes in some B-cell lymphoma/leukemia (e.g., B-CLL, mantle cell lymphoma).
CD7	Pan T-cell marker. Although loss of expression may be observed in some cutaneous T-cell lymphomas, the expression may be downregulated also in cases of inflammatory dermatoses, thus not providing a robust criterion for diagnosis.
CD8	Positive in T-cytotoxic cells.
CD10	CALLA. Positive in neoplastic cells of follicle center lymphomas (follicular > diffuse). Positivity found also in follicular T-helper lymphocytes and derived lymphomas. Positivity in single cells in cutaneous biopsies difficult to evaluate because of background staining of dermal fibers.
CD11c	Marker of normal monocytes/macrophages. Also positive in acute myeloid leukemia and in hairy cell leukemia.
CD13	Marker of myeloid cells. Useful in the diagnosis of myeloid leukemias.
CD14	Marker of monocytes/macrophages. Useful in the diagnosis of myeloid leukemias.
CD15	Hodgkin and Reed-Sternberg cells in Hodgkin lymphoma; Also positive in granulocytes and monocytes and in some myeloid neoplasm.
CD16	Expressed by NK lymphocytes and some T cells.
CD19	Positive in B-cells.
CD20	Positive in B-cells. Expression may be lost after therapy with rituximab.
CD21	Follicular dendritic cells in both benign and malignant infiltrates with lymphoid follicles.
CD23	Positive in the majority of cells of B-CLL; stains also follicular dendritic cells.
CD25	IL-2 receptor, expressed on activated lymphocytes. Positive in ATLL and in some cases of mycosis fungoides. Neoplastic mast cells in systemic mastocytosis are positive for CD25 as well as for CD2.
CD30	Activated T- and B-cells; Hodgkin and Reed-Sternberg cells in Hodgkin lymphoma. Positivity defines a group of cutaneous T-cell lymphomas including cutaneous anaplastic large cell lymphoma and lymphomatoid papulosis. Variable numbers of positive cells may be observed in most cutaneous lymphoproliferative disorders, thus the diagnostic value is only in conjunction with other markers. Positivity required for treatment with brentuximab vedotin.
CD31	Positive in endothelial cells (but not specific for them). Does not discriminate between blood and lymphatic vessels.
CD33	Positive in early myeloid cells, and in subsets of myeloid leukemia.
CD34	Positive in precursor T or B cells and in some case of myeloid leukemia. Positive in endothelial cells (does not discriminate between blood and lymphatic vessels).
CD35	Follicular dendritic cells in both benign and malignant infiltrates with lymphoid follicles.
CD37	Expressed in most T and B cells. May be useful in cases treated with anti-CD37 antibodies (e.g., otlertuzumab).
CD38	Plasma cells in benign and malignant conditions, including plasmablastic lymphoma. Positive in a subset of B-CLL.
CD43	Pan T-cell marker; positive also in myeloid cells. B-cell neoplasms is positive in neoplastic cells of B-CLL and mantle cell lymphoma.
CD45	Leukocyte common antigen (utility in confirming the hematolymphoid origin of a given tumor) (negative in some hematological neoplasms, e.g., plasma cell neoplasms, some anaplastic large cell lymphoma)
CD45RA	Naive T-cells. Positive in primary cutaneous aggressive epidermotropic $CD8^+$ cytotoxic T-cell lymphoma (but diagnosis cannot be based on this marker only).
CD45RO	Memory T-cells. Useful in some cases to confirm T-cell differentiation of neoplastic cells.
CD52	Mature lymphocytes. Positivity is a pre-requisite for treatment with an anti-CD52 antibody (alemtuzumab).
CD54	Intracellular adhesion molecule 1 (ICAM-1). Expressed on endothelial cells. May be implicated in the pathogenesis of intravascular lymphomas.
CD56	Positive in NK-cells and a good marker for the majority of cases of extranodal NK/T-cell lymphoma, nasal-type. Also positive in neoplastic plasma cells.
CD57	Positive in NK-cells (neoplastic cells in extranodal NK/T-cell lymphoma, nasal-type are usually negative)
CD68	Positive in normal and neoplastic histiocytes and macrophages. Positivity in a subset of myeloid leukemias. Two different epitopes marked by the clones KP-1 and PGM-1 may show completely different staining patterns in neoplastic conditions (and sometimes in reactive conditions as well).
CD79a	B-cells. Expression in B lymphocytes starts earlier than that of CD20, thus some precursor B-cell neoplasms may be $CD79a^+$ but $CD20^-$.
CD99	Positive in a subset of precursor cells. Expression is found also in several non-lymphoid neoplasms and should be evaluated only in the general context.
CD103	In cutaneous lymphoproliferative disorders positive mostly in ATLL and in some cases of mycosis fungoides.
CD117	c-kit; positive in both reactive and neoplastic mast cells. Positive in a subset of myeloid leukemias.

Table 1.4 (*cont'd*)

Antigen/antibody	Main immunostaining in cutaneous lymphomas/pseudolymphomas and/or specificity
CD123	Plasmacytoid dendritic cells in both benign and malignant conditions (blastic plasmacytoid dendritic cell neoplasm and dendritic cell neoplasms in chronic myeloid leukemia).
CD138	Plasma cells in benign and malignant conditions, including plasmablastic lymphoma.
CD163	Positive in normal and neoplastic histiocytes and macrophages. More sensitive than CD68. Positivity in a subset of myeloid leukemias.
CD200	Positive in B-cell chronic lymphocytic leukemia.
CD207	Marker of Langerin, specific for Langerhans cells (both benign and malignant).
CD246	ALK-1 (anaplastic large cell lymphoma kinase). Only rarely positive in cases of cutaneous anaplastic large cell lymphoma; positivity may be more common in pediatric cases. The pattern may be nuclear and/or cytoplasmatic, with different patterns associated in part with specific genetic aberrations involving *ALK*.
CD279	PD-1. Positive in follicular T-helper lymphocytes as well as in a subset of activated lymphocytes.
PD-L1	PD-1 ligand. Utility mostly in the setting of specific treatment.
CD303	BDCA2. Expressed in reactive and neoplastic plasmacytoid dendritic cells. Reliable marker of blastic plasmacytoid dendritic cell neoplasm.
Ig heavy chains (IgA, IgD, IgE, IgG, IgM)	B-cells. IgM is important in two main contexts: non-class-switched cutaneous marginal zone lymphoma, and cutaneous diffuse large B-cell lymphoma, leg-type.
IgG4	IgG4-producing plasma cells. Positive in some cutaneous disorders (e.g., granuloma faciale), but not linked with certainty to cutaneous lymphoproliferative disorders.
Ig light-chains (kappa, lambda)	Used to test clonality in infiltrates with prominent B-cell populations; in situ hybridization provides better results but can only be applied in cases with plasma cell differentiation.
Ki-67	Proliferating cells. Useful in two main ways: (i) to determine the proliferation rate (e.g., the proliferation of nearly 100% of neoplastic ells is required for a diagnosis of Burkitt lymphoma), and (ii) to detect the pattern of proliferation and eventual "hot spots" in cases with mixed cell infiltrates. "Aberrant" patterns may be observed in neoplastic lymphoid follicles (decreased proliferation as opposed to the high proliferation typical of reactive follicles), and in band-like T-cell infiltrates related to drugs (very high proliferation as opposed to the low proliferation typical of early mycosis fungoides).
Pan-Cytokeratin	Marker of epithelial cells. Useful in the differential diagnosis of undifferentiated tumors (but it may be aberrantly expressed in non-epithelial neoplasms). Useful also in better visualizing the pattern of intraepithelial lymphocytes, particularly in adnexotropic mycosis fungoides.
EMA	Epithelial membrane antigen. Positive in epithelial tumors and in a subset of lymphocytes and plasma cells. In lymphoproliferative disorders used mainly in multiple myeloma and cutaneous anaplastic large cell lymphoma, but does not give more information than those provided by more specific markers.
S100 protein	Positive in benign and malignant Langerhans cells and in interdigitating reticulum cells. Useful also in the differential diagnosis of dendritic cell proliferations in patients with chronic myeloid neoplasms.
TdT	Terminal deoxynucleotidyl transferase. Nuclear staining (cytoplasmic staining is not specific and mostly due to artifacts, and should be ignored). Positive in precursor lymphomas of both B- and T-cell phenotype. Positivity can be observed in a small subset of myeloid leukemias.
TCR-β (βF1)	α/β T-cells. Positive in some cases of cutaneous γ/δ T-cell lymphoma with expression of both α/β and γ/δ markers. The expression may be lost in some α/β cutaneous T-cell lymphomas, thus negativity cannot be considered as a surrogate for TCR-γ or TCR-δ positivity.
TCR-γ	γ/δ T-cells. Positivity for either TCR-γ or TCR-δ pre-requisite for the diagnosis of cutaneous γ/δ T-cell lymphoma.
TCR-δ	γ/δ T-cells. Positivity for either TCR-γ or TCR-δ pre-requisite for the diagnosis of cutaneous γ/δ T-cell lymphoma.
TIA-1	Present in all cytotoxic T-cells (granular cytoplasmic positivity).
Granzyme-B	Present in activated cytotoxic T-cells (granular cytoplasmic positivity).
Perforin	Present in activated cytotoxic T-cells (granular cytoplasmic positivity).
Bcl-2	Expressed in most mature T- and B-cells. Lack of expression in germinal center B lymphocytes in the lymph nodes is used to confirm benignancy of the germinal centers, but malignant lymphoid follicles in cutaneous follicular lymphoma are mostly Bcl-2-negative. Positivity in neoplastic large B lymphocytes aids in the diagnosis of cutaneous diffuse large B-cell lymphoma, leg-type.
Bcl-6	Nuclear expression in follicular B-cells (both benign and malignant). Positive also in follicular T-helper lymphocytes.
Bcl-10	Nuclear expression in marginal zone lymphoma may be associated with a worse prognosis.
HGAL	B-cells in the germinal center; in general does not provide better information than Bcl-6 in that setting.
LMO-2	B-cells in the germinal center; in general does not provide better information than Bcl-6 in that setting.
IRTA1	Immunoglobulin superfamily receptor translocation-associated 1. Membranous expression. Positive in most cutaneous and other extranodal marginal zone lymphomas; lower percentage of cases of nodal marginal zone lymphoma positive as well.
Anti-HLA-DR	Expression of HLA-DR, a human MHC class II molecule expressed on antigen-presenting cells (subsets of dendritic cells, B lymphocytes, monocytes, macrophages).
CXCL-13	Positive in follicular T-helper lymphocytes and T-cell lymphomas with TFH phenotype.
ICOS	Inducible co-stimulator protein; Positive in follicular T-helper lymphocytes, both benign and malignant.
Cyclin-D1	Uniform positivity in mantle cell lymphoma (a minority of cases is negative); variable numbers of positive cells may be observed in other B-cell neoplasms, particularly plasma cell myeloma.
Cyclin D2, D3	Mantle cell lymphoma (cases negative for cyclin D1).

(*Continued*)

Table 1.4 (*cont'd*)

Antigen/antibody	Main immunostaining in cutaneous lymphomas/pseudolymphomas and/or specificity
SOX11	Mantle cell lymphoma (including cases negative for cyclin D1). Negativity in mantle cell lymphoma linked to a more indolent course.
LEF1	Nuclear expression in B-CLL (negative in mantle cell lymphoma and marginal zone lymphoma)
FOX-P1	Forkhead box protein 1; Nuclear expression in cutaneous diffuse large B-cell lymphoma, leg type (negative in cutaneous follicle center lymphoma, diffuse type).
FOX-P3	Forkhead box protein 3; T-regulatory cells; nuclear expression. Positive in neoplastic cells ATLL and in a subset of cases of mycosis fungoides.
IRF8	Interferon regulatory factor 8. Highly expressed in myeloid cells. Expressed in neoplastic cells of follicle center lymphoma.
IRF4/MUM-1	Multiple myeloma oncogene 1. Positive in plasma cell neoplasms. Useful mostly in the differentiation of cutaneous diffuse large B-cell lymphoma, leg type (positive) from cutaneous follicle center lymphoma, diffuse type (negative or positive in a small minority of cells).
TRAF1	TNF receptor encoded factor 1. Positive in cutaneous CD30$^+$ lymphoproliferative disorders.
ZAP-70	Zeta-associated protein 70. Nuclear positivity in B-CLL is associated with unmutated status and a worse prognosis. Positive also in normal T lymphocytes.
MYC	Overexpression of MYC (nuclear staining). Expression of the antibody is not synonymous with the presence of a chromosomal translocation. Useful in the definition of a subset of diffuse large B-cell lymphoma, leg type with "double" or "triple" expression status (Bcl-2, Bcl-6, MYC). The cut-off point to define positivity is 40% of neoplastic cells.
OCT2	Nuclear expression. Usually used in conjunction with BOB1; positive in most B-cell lymphomas.
BOB1	Nuclear expression. Usually used in conjunction with OCT2; positive in most B-cell lymphomas.
p16	Loss of expression if gene silenced. May have a prognostic value in a subset of cases of cutaneous diffuse large B-cell lymphoma, leg type.
HHV-8	Human herpes virus 8. Positive in all cases of Kaposi sarcoma (both HIV and non-HIV-related). In lymphoproliferative disorders positive in primary effusion lymphoma and a subset of cases of Castleman disease.
EBER-1†	Small nuclear RNA associated with EBV. Nuclear positivity in all cells infected by EBV.
LMP-1	EBV latent membrane protein. Expressed only in latency types 2 and 3, thus does not stain all EBV infected cells.
TP	*Treponema pallidum*, specific for syphilis. The staining pattern reveals the typical morphology of the *Treponema*. The staining should be performed in all cases of lymphoproliferative disorders associated with HIV infection.
Myeloperoxidase	Positive in reactive myeloid cells and in a subset of cases of myeloid leukemia.
MNDA	Myeloid cell nuclear differentiation antigen. Positive in reactive myeloid cells and in a subset of cases of myeloid leukemia. Positive also in a subset of marginal zone lymphoma but negative in cutaneous follicle center lymphoma.
Lysozyme	Positive in reactive myeloid cells and in a subset of cases of myeloid leukemia. Robust marker in cases otherwise negative for most markers.
PAX-5	Paired box gene 5, Immature and mature B-cells. In precursor, B-cell lymphomas may be used as a surrogate marker of CD19 when other B-cell markers are negative. Positive within the nuclei of Hodgkin and Reed-Sternberg cells. A pitfall is represented by positivity for PAX-5 in some cases of Merkel cell carcinoma.
TCL-1	A subset of CD4-/CD8-T-cells. Positive in plasmacytoid dendritic cells. In hematological neoplasms positive in T-cell prolymphocytic leukemia and in blastic plasmacytoid dendritic cell neoplasm.
D2-40	Surrogate marker for podoplanin. Positive in endothelial cells of lymphatic vessels. Crucial for the differential diagnosis of intravascular neoplasms (vessels negative in intravascular B- and NK/T-cell lymphoma, positive in intralymphatic anaplastic large cell lymphoma).
TCF4 (E2-2)	Positive in blastic plasmacytoid dendritic cell neoplasm.
P24	HIV p24-gag viral capsid protein, useful for immunohistochemical demonstration of HIV infection. Positivity is found in follicular dendritic cells and in cutaneous Langerhans cells.
SPIB	Positive in blastic plasmacytoid dendritic cell neoplasm.
Annexin A1	Encoded by the ANXA1 gene which is upregulated in hairy cell leukemia. Considered as the most sensitive and specific marker for the diagnosis of hairy cell leukemia. Expression is mostly membranous, sometimes cytoplasmatic.
NPM1	Aberrant cytoplasmic expression in acute myeloid leukemia with mutated *NPM1*.
FDCSP	Follicular dendritic cell secreted peptide, expressed in follicular dendritic cell sarcoma.
SRGN	Serglycin, expressed in follicular dendritic cell sarcoma.

† In situ hybridization.

cutaneous lymphomas. Early in their differentiation, T and B lymphocytes rearrange their TCR and Ig genes, respectively. Analysis of the gene rearrangement provides clues to the clonality of a given infiltrate. Benign (reactive) lymphoid proliferations are characterized by a polyclonal pattern of TCR and/or Ig gene rearrangement. In contrast, malignant lymphomas reveal a monoclonal population of lymphocytes. A standardized assay (BIOMED-2) has been introduced in order to homogenize the different methods and to allow a better comparison of results of gene rearrangement studies and is still used in most centers [16, 17]. Besides indubitable advantages, analysis of TCR and Ig genes rearrangement also

has limitations. In fact, benign inflammatory dermatoses may present with a monoclonal pattern, and a "germline" or polyclonal pattern may be observed in clear-cut lymphomas (e.g., in NK-cell neoplasms or in blastic plasmacytoid dendritic cell neoplasms, among others). In addition, the presence of only a few neoplastic cells may give rise to false negative results in cases of early cutaneous T- or B-cell lymphoma, and the finding of small clones of reactive lymphocytes may be falsely interpreted as a monoclonal population of cells in benign infiltrates ("pseudoclonality"). Next-generation sequencing (NGS), known also as "high-throughput sequencing" has been proposed as a more reliable method for analysis of T-cell clonality [18–20]. This technique provides indubitable advances over standard polymerase chain reaction (PCR) protocols, providing also data on the quantity of neoplastic cells present in a given infiltrate. In a recent overview of published literature, the sensitivity of NGS ranged between 69% and 100% (sensitivity of standard PCR methods was 44–72%), and specificity ranged between 86% and 100% (specificity of standard PCR methods was 77–88%) [21], thus showing an improvement in the diagnostic utility compared to standard methods. On the other hand, data from non-lymphoma patients (i.e., patients with inflammatory conditions) are still scarce, and the method is expensive, and not yet widely accessible.

Other methods used in the study of cutaneous lymphoid infiltrates

Fluorescence in situ hybridization (FISH)

The fluorescence in situ hybridization (FISH) technique is based on the annealing of single-stranded DNA to a complementary genomic target sequence in a neoplastic cell. Depending on the probes selected, the FISH method can be used to detect different types of chromosomal abnormalities, including monosomy, trisomy, and other aneuploidies, as well as translocations and deletions. This method can be used routinely and can provide valuable information for precise diagnosis and classification.

There are two main types of probes for the detection of translocations, namely, dual-fusion and break-apart probes [22]. Dual-fusion probes consist of two probes labeled in different colors, each of them binding to a distinct chromosome. They are designed to detect translocations of part of one chromosome to another chromosome. In cells not bearing the translocation that is being investigated, four distinct signals (two for each color) are recognized, corresponding to the two alleles of each separate chromosome. By contrast, cells bearing the translocation will show two distinct signals (one for each color), corresponding to the intact alleles, and two fused signals, corresponding to the translocated chromosomes. Dual-fusion probes are highly specific, the main limitation being that they recognize only the translocation for which they have been designed. They are particularly useful for the detection of translocations that are common in a given lymphoma (e.g., the t(14;18) in nodal follicle center lymphoma). Break-apart probes consist of two distinct probes labeled in different colors, binding to DNA sequences flanking the known region of a chromosome. If the region is split, then two signals appear separated, representing the split chromosome, and two are together, representing the normal allele. If the region is intact, four close signals represent the two alleles of the chromosome without breaks. Break-apart probes are very sensitive for detecting chromosomal splits, but do not provide any information concerning the other gene involved in the translocation. They are particularly useful in lymphomas that show different translocations involving one part of a given chromosome with various partner chromosomes (this is the case, for example, for *MYC* translocations).

Other molecular investigations

A detailed discussion of molecular techniques used in the study of cutaneous lymphomas is beyond the scope of this book. Besides, methods that seem to be innovative at the time of writing may be obsolete when the book is out in print. In addition, cost and availability are still a limiting factor, as most dermatopathology laboratories are not equipped with molecular techniques, or have only limited possibilities. With the exception of analysis of TCR and Ig genes rearrangement and of FISH techniques, genomic analyses cannot yet be considered routine in the diagnosis of cutaneous lymphomas in most dermatopathological laboratories. On the other hand, new genetic insights into malignant tumors are providing not only diagnostic clues but also allowing the identification of molecules that represent potential therapeutic targets [23]. Genetic and epigenetic alterations relevant to different types of cutaneous T- and B-cell lymphomas will be discussed in the respective chapters. A review of molecular techniques useful in hematopathology (that is, not only for cutaneous lymphomas) has been recently published [24].

Lymphoma microenvironment and lymphoma-associated microorganisms

Lymphomas are not constituted by pure populations of malignant lymphocytes, and the presence of accessory (non-neoplastic) cells admixed with neoplastic ones is well known. In mycosis fungoides, for example, a population of interdigitating reticulum cells has been observed in specific lesions, and several studies demonstrated that their number varies in different stages of the disease, decreasing in more advanced stages. There is good evidence that non-neoplastic lymphoid and other accessory cells are crucial for the development and maintenance

of malignant lymphomas, particularly low-grade ones, and a large number of such cells has been identified and better characterized ("lymphoma microenvironment"). The interaction of neoplastic cells with their microenvironment is a two-way relationship: the microenvironment helps in sustaining the neoplastic cells and at the same time malignant lymphocytes recruit accessory and other reactive cells. A typical example is represented by angioimmunoblastic T-cell lymphoma, a peculiar neoplasm deriving from specific subsets of follicular T-helper (TFH) lymphocytes with a $CD4^+$/$PD\text{-}1^+$/$Bcl\text{-}6^+$/$CXCL\text{-}13^+$/$ICOS^+$ phenotype, which is invariably associated with a reactive compartment of B lymphocytes and other accessory cells.

Besides accessory cells, in many lymphomas, a pivotal role is played by microorganisms, particularly viruses. The Epstein–Barr virus (EBV) is involved in several types of lymphomas, and the demonstration of EBV integration in neoplastic cells is an important diagnostic criterion in many lymphoma types. Besides EBV, other viruses are involved in some lymphoproliferative conditions (e.g., human herpes virus (HHV)-8 and human T-lymphotropic virus 1 (HTLV-1)). Bacteria, too, have been implicated in the etiology of some cases of non-Hodgkin lymphoma (e.g., *Borrelia burgdorferi* in cutaneous marginal zone lymphoproliferative disorder, *Helicobacter pylori* in gastric MALT-lymphoma). In short, several microorganisms are linked to different types of lymphoproliferative conditions, and demonstration of infection is important for both diagnosis and (sometimes) treatment.

Pseudomalignancy, premalignancy, and early malignancy

One of the major conceptual problems in the field of cutaneous lymphomas is the precise classification of "early" manifestations of it, and their distinction from benign infiltrates. The concept of the "parapsoriases," introduced by the French dermatologist Brocq in 1902, is paradigmatic of this problem and shows that, in spite of over 100 years of research, we are still unable to provide a precise conceptual frame for "pseudo" malignancies, "pre" malignancies, and "early" malignancies (see also Chapter 2) [25, 26]. This difficulty is not unique to cutaneous lymphomas (actinic keratosis and melanoma in situ represent two other typical examples), and is not confined to skin neoplasms, but rather is an intrinsic problem of most "cancers."

In my opinion, some of the difficulties that we encounter in daily routine in the diagnosis of early cutaneous lymphomas are, in truth, conceptual rather than practical: the search for criteria that allow diagnosis of the earliest stages of malignant tumors brings us to the grey zone between clearly benign and clearly malignant neoplasms, in a cloudy area where conventional definitions and criteria do not always work. Increased knowledge and improved diagnostic techniques are changing the very concept of cancer, not only in the skin but in other organs as well. Autopsy investigations of men older than 80 years demonstrated that nearly all of them have small prostatic carcinomas that were clinically silent and that did not affect their life span. In fact, it seems likely that in many (if not all) organs there are forms of early cancer that are clinically silent and that do not cause overt disease. This problem is well known to epidemiologists, and is defined as "over diagnosis" of cancer, thereby meaning not a false positive result (i.e., a wrong diagnosis of cancer) but a diagnosis of a tumor that fulfills all pathologic criteria of cancer, but that would not have grown to become clinically evident [27]. In short, the major difficulty lies in defining precisely what is early cancer and in drawing an unambiguous line between what is clearly benign and what is already malignant.

In the realm of lymphoproliferative disorders, a paradigmatic example of the problem of drawing a precise line between "benignancy" and "malignancy" is represented by monoclonal gammopathy of undetermined significance (MGUS). Patients with MGUS are at risk of progression into a lymphoproliferative malignancy (usually a plasma cell myeloma). On the other hand, it has been demonstrated that, although not all patients with MGUS develop malignant lymphoma, almost all patients with multiple myeloma had a preceding MGUS, thus clearly showing that this is more an "early malignancy" than a "non-neoplastic" process. To further complicate the issue, the concept of "monoclonal gammopathy of clinical significance" has been introduced [28], again splitting the "grey area" into small "entities" with different names, all of which reflect different stages of the same pathological process. Similar conceptual problems in hematology are represented by monoclonal B-cell lymphocytosis, follicular lymphoma "in situ," myelodysplastic syndromes, clonal hematopoiesis of indeterminate potential and other "borderline" conditions, and in the skin by "parapsoriasis en plaques" and lymphomatoid papulosis, among others. There is sufficient evidence that not all "early malignant" tumors must invariably progress to metastatic disease and kill the patient, and in my opinion, our main difficulty is probably more of a semantic nature, namely, the exact definition (and nomenclature) of what is "early" cancer.

So where do we draw the line? Where do we set the boundary between benign and malignant diseases? In my opinion, any boundary – like any classification – is clearly arbitrary and artificial. On the other hand, in order to treat patients we need classifications, precise diagnostic criteria, and clear-cut boundaries between diseases. In this context, it should be unambiguously stated that our definitions and criteria work in the vast majority of cases of cutaneous lymphoma (and, of course, of other diseases as well). In patients with "borderline" disorders, a pragmatic approach seems to be the most appropriate, avoiding unnecessary aggressive treatment. What is radically changing, on the other hand, is the concept of "early cancer" and the way we convey this diagnosis to our patients. It is the responsibility of managing physicians to provide accurate information to their patients, clearly explaining to them the problems related to a

diagnosis of "parapsoriasis" or early mycosis fungoides, as well as the existence and the meaning of the "grey zone" between benign and malignant conditions.

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