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 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 28.

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 26.

Classification of cutaneous lymphomas

The World Health Organization (WHO) published in 2017 the last revision of the *Classification of Tumours of Haematopoietic and Lymphoid Tissues* (Table 1.1) [1]. Since several years the WHO scheme is used worldwide, replacing all former classification systems (older readers will still remember the plethora of different classifications that were used in the past, representing the source of huge problems when comparing data from different centers). For what concerns cutaneous lymphomas, the WHO scheme is based on the seminal work made by the European Organization for Research and Treatment of Cancer (EORTC) Cutaneous Lymphoma Task Force, which in 1997 published the first comprehensive classification of cutaneous lymphomas [2], subsequently revised together with a WHO panel in 2005 and 2018 (Table 1.2) [3].

Despite the presence of an accepted frame for classification of primary cutaneous lymphomas, in many publications, an 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. It is paramount that physicians in different countries and centers speak one and the same scientific "language," and the WHO and EORTC–WHO classifications provide the basis for classifying cases in the same manner, irrespective of the country where patients are managed.

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.

COPYRIGHTED MATERIAL

Skin Lymphoma: The Illustrated Guide, Fifth Edition. Lorenzo Cerroni.
© 2020 John Wiley & Sons Ltd. Published 2020 by John Wiley & Sons Ltd.

Table 1.1 Revised 4th edition of the WHO *Classification of Tumours of Haematopoietic and Lymphoid Tissues* (2017)

Myeloproliferative neoplasms
Chronic myeloid leukemia, *BCR-ABL1*–positive
Chronic neutrophilic leukemia
Polycythemia vera
Primary myelofibrosis
Essential thrombocythemia
Chronic eosinophilic leukemia, NOS
Myeloproliferative neoplasm, unclassifiable

Mastocytosis
Cutaneous mastocytosis
Systemic mastocytosis
Indolent systemic mastocytosis
Mast cell sarcoma

Myeloid/lymphoid neoplasms with eosinophilia and gene rearrangement
Myeloid/lymphoid neoplasms with *PDGFRA* rearrangement
Myeloid/lymphoid neoplasms with *PDGFRB* rearrangement
Myeloid/lymphoid neoplasms with *FGFR1* rearrangement
Myeloid/lymphoid neoplasms with PCM1-JAK2 9968/3

Myelodysplastic/myeloproliferative neoplasms
Chronic myelomonocytic leukemia
Atypical chronic myeloid leukemia, *BCR-ABL1*–negative
Juvenile myelomonocytic leukemia
Myelodysplastic/myeloproliferative neoplasm with ring sideroblasts and thrombocytosis
Myelodysplastic/myeloproliferative neoplasm, unclassifiable

Myelodysplastic syndromes
Myelodysplastic syndrome with single lineage dysplasia
Myelodysplastic syndrome with ring sideroblasts and single lineage dysplasia
Myelodysplastic syndrome with ring sideroblasts and multilineage dysplasia
Myelodysplastic syndrome with multilineage dysplasia
Myelodysplastic syndrome with excess blasts
Myelodysplastic syndrome with isolated del(5q)
Myelodysplastic syndrome, unclassifiable
Refractory cytopenia of childhood (provisional entity)

Myeloid neoplasms with germline predisposition
Acute myeloid leukemia with germline *CEBPA* mutation
Myeloid neoplasms with germline *DDX41* mutation
Myeloid neoplasms with germline *RUNX1* mutation
Myeloid neoplasms with germline *ANKRD26* mutation
Myeloid neoplasms with germline *ETV6* mutation
Myeloid neoplasms with germline *GATA2* mutation
Acute myeloid leukemia (AML) and related precursor neoplasms
AML with recurrent genetic abnormalities
AML with t(8;21)(q22;q22.1); *RUNX1-RUNX1T1*
AML with inv.(16)(p13.1q22) or t(16;16)(p13.1;q22); *CBFB-MYH11*
Acute promyelocytic leukemia with *PML-RARA*
AML with t(9;11)(p21.3;q23.3); *KMT2A-MLLT3*
AML with t(6;9)(p23;q34.1); *DEK-NUP214*
AML with inv.(3)(q21.3q26.2) or t(3;3)(q21.3;q26.2); *GATA2*, *MECOM*
AML (megakaryoblastic) with t(1;22)(p13.3;q13.1); *RBM15-MKL1*
AML with BCR-ABL1 (provisional entity)
AML with mutated NPM1
AML with biallelic mutation of *CEBPA*
AML with mutated RUNX1 (provisional entity)
AML with myelodysplasia-related changes
Therapy-related myeloid neoplasms
Acute myeloid leukaemia, NOS
AML with minimal differentiation
AML without maturation
AML with maturation
Acute myelomonocytic leukemia
Acute monoblastic and monocytic leukemia
Pure erythroid leukemia
Acute megakaryoblastic leukemia
Acute basophilic leukemia
Acute panmyelosis with myelofibrosis
Myeloid sarcoma (may present primary in the skin)
Myeloid proliferations associated with Down syndrome
Transient abnormal myelopoiesis associated with Down syndrome
Myeloid leukemia associated with Down syndrome

Blastic plasmacytoid dendritic cell neoplasm (often presents primary in the skin)
Acute leukemias of ambiguous lineage
Acute undifferentiated leukemia
Mixed-phenotype acute leukemia with t(9;22)(q34.1;q11.2); *BCR-ABL1*
Mixed-phenotype acute leukemia with t(v;11q23.3); *KMT2A*-rearranged
Mixed-phenotype acute leukemia, B/myeloid, NOS
Mixed-phenotype acute leukemia, T/ myeloid, NOS
Mixed-phenotype acute leukemia, NOS, rare types
Acute leukemias of ambiguous lineage, NOS

Precursor lymphoid neoplasms
B-lymphoblastic leukemia/lymphoma, NOS (may present primary in the skin)
B-lymphoblastic leukemia/lymphoma with recurrent genetic abnormalities
B-lymphoblastic leukemia/lymphoma with t(9;22)(q34.1;q11.2); *BCR-ABL1*
B-lymphoblastic leukemia/lymphoma with t(v;11q23.3); *KMT2A*-rearranged
B-lymphoblastic leukemia/lymphoma with t(12;21)(p13.2;q22.1); *ETV6-RUNX1*
B-lymphoblastic leukemia/lymphoma with hyperdiploidy
B-lymphoblastic leukemia/lymphoma with hypodiploidy (hypodiploid ALL)
B-lymphoblastic leukemia/lymphoma with t(5;14)(q31.1;q32.1); IGH/*IL3*
B-lymphoblastic leukemia/lymphoma with t(1;19)(q23;p13.3); *TCF3-PBX1*
B-lymphoblastic leukemia/lymphoma, BCR-ABL1–like (provisional entity)
B-lymphoblastic leukemia/lymphoma with iAMP21
T-lymphoblastic leukemia/lymphoma
Early T-cell precursor acute lymphoblastic leukemia
NK-lymphoblastic leukemia/lymphoma (provisional entity)

Mature B-cell neoplasms
Chronic lymphocytic leukemia (CLL)/small lymphocytic lymphoma
Monoclonal B-cell lymphocytosis
  CLL type
  Non-CLL type
B-cell prolymphocytic leukemia
Splenic marginal zone lymphoma
Hairy cell leukemia
Splenic B-cell lymphoma/leukemia, unclassifiable
  Splenic diffuse red pulp small B-cell lymphoma (provisional entity)
  Hairy cell leukemia variant (provisional entity)
Lymphoplasmacytic lymphoma
Monoclonal gammopathy of undetermined significance, IgM
Heavy chain diseases
  μ Heavy chain disease
  γ Heavy chain disease
  α Heavy chain disease
Plasma cell neoplasms
  Non-IgM monoclonal gammopathy of undetermined significance
  Plasma cell myeloma
    Plasma cell myeloma variants
Plasmacytoma
  Solitary plasmacytoma of bone
  Extraosseous plasmacytoma
Monoclonal immunoglobulin deposition diseases
  Primary amyloidosis

Table 1.1 (*cont'd*)

- Light chain and heavy chain deposition diseases
- Plasma cell neoplasms with associated paraneoplastic syndrome
  - POEMS syndrome
  - TEMPI syndrome (provisional entity)
- *Extranodal marginal zone lymphoma of mucosa-associated lymphoid tissue (MALT lymphoma) (includes primary cutaneous marginal zone lymphoma)*
- Nodal marginal zone lymphoma
  - Pediatric nodal marginal zone lymphoma
- Follicular lymphoma
  - In situ follicular neoplasia
  - Duodenal-type follicular lymphoma 9690/3
- Pediatric-type follicular lymphoma
- Large B-cell lymphoma with IRF4 rearrangement (provisional entity)
- *Primary cutaneous follicle center lymphoma*
- Mantle cell lymphoma
  - Leukemic non-nodal mantle cell lymphoma
  - In situ mantle cell neoplasia
- Diffuse large B-cell lymphoma (DLBCL), NOS
  - Germinal center B-cell subtype
  - Activated B-cell subtype
- T-cell/histiocyte-rich large B-cell lymphoma
- Primary DLBCL of the CNS
- *Primary cutaneous DLBCL, leg type*
- EBV-positive DLBCL, NOS
- *EBV-positive mucocutaneous ulcer*
- DLBCL associated with chronic inflammation
- Lymphomatoid granulomatosis
  - Grade 1 or 2
  - Grade 3
- Primary mediastinal (thymic) large B-cell lymphoma
- *Intravascular large B-cell lymphoma (often presents primary in the skin)*
- ALK-positive large B-cell lymphoma
- Plasmablastic lymphoma
- Primary effusion lymphoma
- HHV8-associated lymphoproliferative disorders
  - Multicentric Castleman disease
  - HHV8-positive DLBCL, NOS
  - HHV8-positive germinotropic lymphoproliferative disorder
- Burkitt lymphoma
- Burkitt-like lymphoma with 11q aberration (provisional entity)
- High-grade B-cell lymphoma
- High-grade B-cell lymphoma with *MYC* and *BCL2* and/or *BCL6* rearrangement
- High-grade B-cell lymphoma, NOS
- B-cell lymphoma, unclassifiable, with features intermediate between DLBCL and classic Hodgkin lymphoma

Mature T- and NK-cell neoplasms

- T-cell prolymphocytic leukemia
- T-cell large granular lymphocytic leukemia
- Chronic lymphoproliferative disorder of NK cells (provisional entity)
- Aggressive NK-cell leukemia
- EBV-positive T-cell lymphoproliferative diseases of childhood
  - Systemic EBV-positive T-cell lymphoma of childhood
  - Chronic active EBV infection of T- and NK-cell type, systemic form
  - *Hydroa vacciniforme-like lymphoproliferative disorder*
  - *Severe mosquito bite allergy*
- *Adult T-cell leukemia/lymphoma (may present primary in the skin)*
- *Extranodal NK/T-cell lymphoma, nasal type (may present primary in the skin)*
- Intestinal T-cell lymphoma
  - Enteropathy-associated T-cell lymphoma
  - Monomorphic epitheliotropic intestinal T-cell lymphoma
  - Intestinal T-cell lymphoma, NOS
  - Indolent T-cell lymphoproliferative disorder of the gastrointestinal tract (provisional entity)
- Hepatosplenic T-cell lymphoma
- *Subcutaneous panniculitis-like T-cell lymphoma*
- *Mycosis fungoides*
- *Sézary syndrome*
- *Primary cutaneous CD30-positive T-cell lymphoproliferative disorders*
  - *Lymphomatoid papulosis*
  - *Primary cutaneous anaplastic large cell lymphoma*
- *Primary cutaneous peripheral T-cell lymphomas, rare subtypes*
  - *Primary cutaneous gamma delta T-cell lymphoma*
  - *Primary cutaneous CD8-positive aggressive epidermotropic cytotoxic T-cell lymphoma (provisional entity)*
  - *Primary cutaneous acral CD8-positive T-cell lymphoma (provisional entity)*
  - *Primary cutaneous CD4-positive small/medium T-cell lymphoproliferative disorder (provisional entity)*
- *Peripheral T-cell lymphoma, NOS (may present primary in the skin)*
- **Angioimmunoblastic T-cell lymphoma and other nodal lymphomas of T follicular helper cell origin**
  - Angioimmunoblastic T-cell lymphoma
  - Follicular T-cell lymphoma
  - Nodal peripheral T-cell lymphoma with T follicular helper phenotype
- Anaplastic large cell lymphoma, ALK-positive
- Anaplastic large cell lymphoma, ALK-negative
- Breast implant-associated anaplastic large cell lymphoma (provisional entity)

Hodgkin lymphomas

- Nodular lymphocyte-predominant Hodgkin lymphoma
- Classic Hodgkin lymphoma
  - Nodular sclerosis classic Hodgkin lymphoma
  - Lymphocyte-rich classic Hodgkin lymphoma
  - Mixed cellularity classic Hodgkin lymphoma
  - Lymphocyte-depleted classic Hodgkin lymphoma

Immunodeficiency-associated lymphoproliferative disorders (may present primary in the skin)

- Lymphoproliferative diseases associated with primary immune disorders
- Lymphomas associated with HIV infection
- Posttransplant lymphoproliferative disorders (PTLDs)
  - Nondestructive PTLDs
  - Plasmacytic hyperplasia PTLD
  - Infectious mononucleosis PTLD
  - Florid follicular hyperplasia PTLD
  - Polymorphic PTLD
  - Monomorphic PTLDs (B- and T/NK-cell types)
  - Classic Hodgkin lymphoma PTLD
  - Other iatrogenic immunodeficiency-associated lymphoproliferative disorders

Histiocytic and dendritic cell neoplasms (may present primary in the skin)

- Histiocytic sarcoma
- Tumors derived from Langerhans cells
  - Langerhans cell histiocytosis
  - Langerhans cell sarcoma
- Indeterminate dendritic cell tumor
- Interdigitating dendritic cell sarcoma
- Follicular dendritic cell sarcoma
  - Inflammatory pseudotumor-like follicular/fibroblastic dendritic cell sarcoma
- Fibroblastic reticular cell tumor
- Disseminated juvenile xanthogranuloma
- Erdheim–Chester disease

Italic, primary cutaneous lymphomas.
Adapted from Swerdlow *et al*. [1].

Table 1.2 Revised 2018 WHO–EORTC classification of primary cutaneous lymphomas

Cutaneous T-cell lymphomas
Mycosis fungoides
Folliculotropic mycosis fungoides
Pagetoid reticulosis
Granulomatous slack skin
Sézary syndrome
Adult T-cell leukemia/lymphoma
Primary cutaneous CD30⁺ lymphoproliferative disorders
Cutaneous anaplastic large cell lymphoma
Lymphomatoid papulosis
Subcutaneous panniculitis-like T-cell lymphoma
Extranodal NK/T-cell lymphoma, nasal type
Chronic active EBV infection
Primary cutaneous peripheral T-cell lymphoma, rare subtypes
Primary cutaneous γ/δ T-cell lymphoma
CD8⁺ aggressive epidermotropic cytotoxic T-cell lymphoma
Primary cutaneous CD4⁺ small/medium T-cell lymphoproliferative disorder
Primary cutaneous acral CD8⁺ T-cell lymphoma
Primary cutaneous peripheral T-cell lymphoma, not otherwise specified
Cutaneous B-cell lymphomas
Primary cutaneous marginal zone lymphoma
Primary cutaneous follicle center lymphoma
Primary cutaneous diffuse large cell lymphoma, leg type
EBV⁺ mucocutaneous ulcer
Intravascular large B-cell lymphoma

Adapted from Willemze *et al*. [2] (American Society of Hematology). Provisional entities are in italic.

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 bone marrow biopsy in patients with primary cutaneous marginal zone lymphoma is also questionable [4], and I do not suggest to perform it in otherwise asymptomatic patients.

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 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. 1.2a–c). 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 valid information on specimens with drying artifacts, but as a morphologic-phenotypic correlation is no longer possible, the histologic report should mention that evaluation of immunohistology is seriously hindered by the artifacts (Fig. 1.2d). 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 theater), and cauterization artifacts (due to the use of cauterizing surgical blades – so-called harmonic scalpels). It is imperative that dermatological surgeons, when submitting specimens with such artifacts, get proper information from referring colleagues 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.

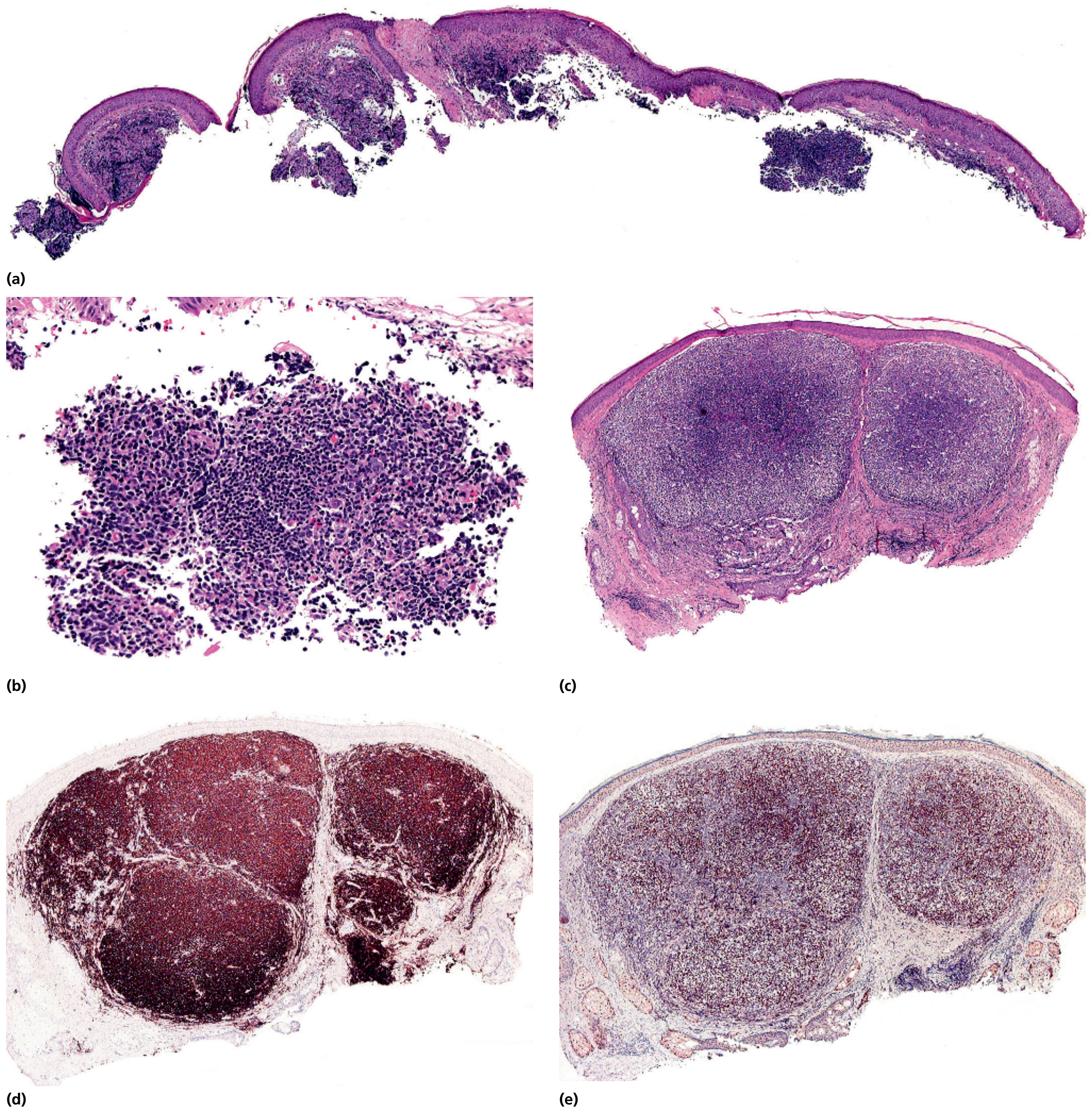

Figure 1.1 Surgical artifact due to a superficial shave biopsy. (a) Superficial shave biopsy taken from the nose under the clinical diagnosis of "r/o basal cell carcinoma" revealed a flat epidermis and fragments of lymphoid infiltrates; (b) some of the cells within the infiltrate had large nuclei, and 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 and (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 nodular lymphoid infiltrate than a shave biopsy (a shave biopsy may be used for superficial infiltrates).

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.)

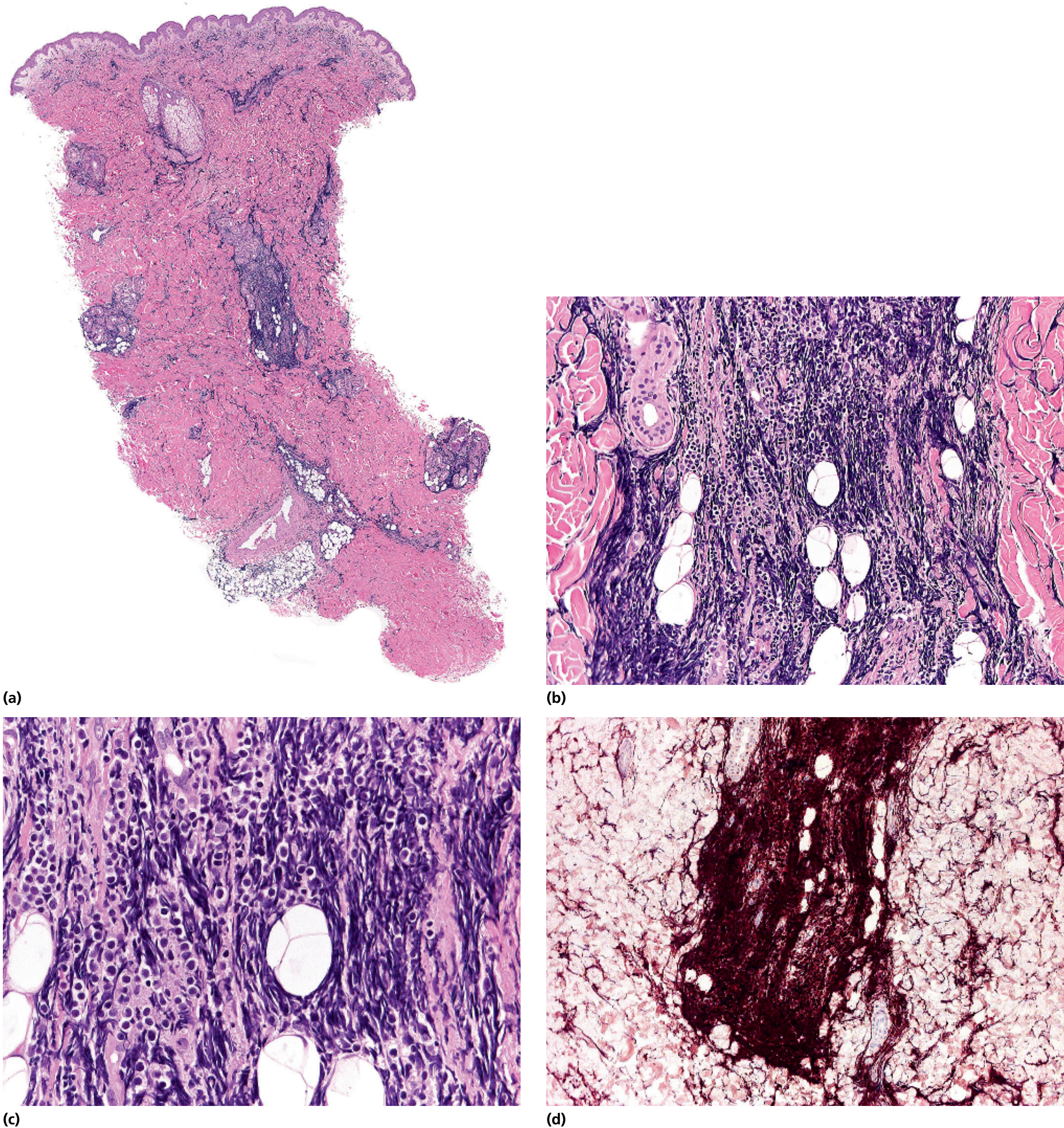

Figure 1.2 Surgical artifact due to placing the biopsy on a gauze. (a) A 4-mm punch biopsy originally well taken and deep enough (b) shows at high power severe drying artifacts that affect most of the neoplastic cells within the infiltrate; (c) some of the evaluable cells show a mid-sized blastoid appearance.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

Much information can be gathered at low power by examination of the pattern of growth, and basic morphologic assessment is useful also for 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 standardization of phenotypic studies on formalin-fixed paraffin-embedded (FFPE) tissue sections. A list of antibodies reactive with lymphocyte subsets and accessory cells

in FFPE tissue sections is provided in Table 1.3. 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 and cheaper and gives better information in order to establish the diagnosis. Sometimes, however, a staining for pan-T-cell markers may be useful in better displaying the number and distribution of intraepithelial lymphocytes.

Although phenotypic investigations provide crucial information for 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, evolution of a tumor into a clonally related neoplasm of a different cell line, have been described [5]. 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 [6]. 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 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 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 [7].

Table 1.3 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
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

(Continued)

Table 1.3 (*cont'd*)

Antigen/antibody	Main immunostaining in cutaneous lymphomas/pseudolymphomas and/or specificity
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. In B-cell neoplasm 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 prerequisite for treatment with 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 nonlymphoid 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
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 to 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: (a) to determine the proliferation rate (e.g., proliferation of nearly 100% of neoplastic cells is required for a diagnosis of Burkitt lymphoma) and (b) 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

Table 1.3 (cont'd)

Antigen/antibody	Main immunostaining in cutaneous lymphomas/pseudolymphomas and/or specificity
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 subsets 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. 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 prerequisite for the diagnosis of cutaneous γ/δ T-cell lymphoma
TCR-δ	γ/δ T cells. Positivity for either TCR-γ or TCR-δ prerequisite 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 T_{FH} 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)
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 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	Tumor necrosis factor (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 worse prognosis. Positive also in normal T lymphocytes
MYC	Overexpression of MYC (nuclear staining). Expression of the antibody is not synonymous of 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 and 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

(Continued)

Table 1.3 (*cont'd*)

Antigen/antibody	Main immunostaining in cutaneous lymphomas/pseudolymphomas and/or specificity
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 of some cases of Merkel cell carcinoma
TCL-1	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 that 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*
GATA3	A transcription factor that is encoded by the *GATA3* gene; useful in the subclassification of peripheral T-cell lymphoma, NOS in the lymph nodes
TBX21	T-box transcription factor is a protein encoded by the *TBX21* gene; useful in the subclassification of peripheral T-cell lymphoma, NOS in the lymph nodes
CCR4	C–C chemokine receptor type 4 is a protein encoded by the *CCR4* gene; useful in the subclassification of peripheral T-cell lymphoma, NOS in the lymph nodes
CD183	Recognizes CXCR3, a chemokine receptor in the CXC chemokine receptor family; useful in the subclassification of peripheral T-cell lymphoma, NOS in the lymph nodes

* In situ hybridization.

Gene rearrangement studies

Analysis of the T-cell receptor (TCR) and immunoglobulin (Ig) genes provides useful information for the study of 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 [8, 9]. Besides indubitable advantages, analysis of *TCR* and *Ig* gene 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"). Recently, high-throughput sequencing has been proposed as a more reliable method for analysis of T-cell clonality [10–12]. This technique provides indubitable advances over standard PCR protocols, providing also data on the quantity of neoplastic cells present in a given infiltrate. On the other hand, specificity (i.e., data on results in reactive cutaneous conditions) has not yet been adequately investigated.

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 [13]. 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 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, e.g., for *MYC* translocations).

Other genetic investigations

A detailed discussion of genetic 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* gene rearrangement and of FISH techniques, genomic analyses cannot yet be considered routine in the diagnosis of cutaneous lymphomas. On the other hand, new genetic insights in malignant tumors are not only providing diagnostic clues but also allowing the identification of molecules that represent potential therapeutic targets.

Lymphoma microenvironment and lymphoma-associated microorganisms

Lymphomas are not constituted by pure populations of malignant lymphocytes, and the presence of accessory (nonneoplastic) 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 nonneoplastic lymphoid and other accessory cells are crucial for the development and maintenance of malignant lymphomas, particularly of 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 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 lymphoma, *Helicobacter pylori* in gastric MALT lymphoma). In short, several microorganisms are linked to different types of lymphoma, 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) [14, 15]. 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 gray 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 also 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 “overdiagnosis” 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 [16]. In short, the major difficulty lies in defining precisely what is an 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 a malignant lymphoma, almost all patients with multiple myeloma had a preceding MGUS, thus clearly showing that this is more an “early malignancy” than a “nonneoplastic” process. To further complicate the issue, the concept of “monoclonal gammopathy of clinical significance” has been introduced [17], again splitting the “gray 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 of what is an “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 “gray zone” between benign and malignant conditions.

References

1. Swerdlow SH, Campo E, Harris NL, *et al*., eds. *WHO Classification of Tumours of Haematopoietic and Lymphoid Tissues*. Revised 4th edition. Lyon: IARC Press, 2017.
2. Willemze R, Kerl H, Sterry W, *et al*. EORTC classification for primary cutaneous lymphomas: a proposal from the Cutaneous Lymphoma Study Group of the European Organization for Research and Treatment of Cancer. *Blood* 1997;**90**:354–371.
3. Willemze R, Cerroni L, Kempf W, *et al*. The 2018 update of the WHO-EORTC classification for primary cutaneous lymphomas. *Blood* 2019;**133**:1703–1714.
4. Senff NJ, Kluin-Nelemans JC, Willemze R. Results of bone marrow examination in 275 patients with histological features that suggest an indolent type of cutaneous B-cell lymphoma. *Br J Haematol* 2008;**142**:52–56.
5. Kumar R, Khan SP, Joshi DD, *et al*. Pediatric histiocytic sarcoma clonally related to precursor B-cell acute lymphoblastic leukemia with homozygous deletion of CDKN2A encoding p16INK4A. *Pediatr Blood Cancer* 2011;**56**:307–310.
6. West DS, Dogan A, Quint PS, *et al*. Clonally related follicular lymphomas and Langerhans cell neoplasms – expanding the spectrum of transdifferentiation. *Am J Surg Pathol* 2013;**37**:978–986.
7. Montecino-Rodriguez E, Leathers H, Dorshkind K. Bipotential B-macrophage progenitors are present in adult bone marrow. *Nat Immunol* 2001;**2**:83–88.
8. Van Dongen JJM, Langerak AW, Brüggemann M, *et al*. Design and standardization of PCR primers and protocols for detection of clonal immunoglobulin and T-cell receptor gene recombinations in suspect lymphoproliferations: report of the BIOMED-2 Concerted Action BMH4-CT98-3936. *Leukemia* 2003;**17**:2257–2317.
9. Van Krieken JH, Langerak AW, Macintyre EA, *et al*. Improved reliability of lymphoma diagnostics via PCR-based clonality testing: report of the BIOMED-2 Concerted Action BHM4-CT98-3936. *Leukemia* 2007;**21**:201–206.
10. Scherer F, Kurtz DM, Diehn M, Alizadeh AA. High-throughput sequencing for noninvasive disease detection in hematologic malignancies. *Blood* 2017;**130**:440–452.
11. Kirsch IR, Watanabe R, O'Malley JT, *et al*. TCR sequencing facilitates diagnosis and identifies mature T cells as the cell of origin in CTCL. *Sci Transl Med* 2015;**7**:308ra158.
12. Matos TR, de Rie MA, Teunissen MBM. Research techniques made simple: high-throughput sequencing of the T-cell receptor. *J Invest Dermatol* 2017;**137**:e131–e138
13. Ventura RA, Martin-Subero JI, Jones M, *et al*. FISH analysis for the detection of lymphoma-associated chromosomal abnormalities in routine paraffin-embedded tissue. *J Mol Diagn* 2006;**8**:141–151.
14. Cerroni L. Cutaneous lymphoid proliferations: a clinicopathological continuum? *Diagn Histopathol* 2009;**16**:417–424.
15. Ganapathi KA, Pittaluga S, Odejide OO, *et al*. Early lymphoid lesions: conceptual diagnostic and clinical challenges, *Haematologica* 2014;**99**:1421–1432.
16. Welch HG, Black WC. Overdiagnosis in cancer. *J Natl Cancer Inst* 2010;**102**:605–613.
17. Fermand JP, Bridoux F, Dispenzieri A, *et al*. Monoclonal gammopathy of clinical significance: a novel concept with therapeutic implications. *Blood* 2018;**132**:1478–1485.