Practical evaluation and management of cutaneous lymphoma

Maxwell A. Fung, MD, Michael J. Murphy, MD, Diane M. Hoss, MD, and Jane M. Grant-Kels, MD
Farmington, Connecticut

Accurate evaluation of patients with suspected or known cutaneous lymphoma requires the integration of many sources and types of information, including clinical evaluation, microscopic analysis of tissue, immunophenotyping, gene rearrangement studies, clinical staging, and longitudinal observation. Diagnoses should be based on knowledge of specific lymphoma types as described in modern classification systems. Management of patients with cutaneous lymphoma requires collaboration among dermatologists, dermatopathologists, hematopathologists, and medical, surgical and radiation oncologists. (J Am Acad Dermatol 2002;46:325-57.)

Learning objective: At the conclusion of this learning activity, participants should better understand how to evaluate and manage patients for suspected or established lymphoma of the skin. Components include the clinical history and physical examination, optimal biopsy and tissue handling, interpretation of pathology and adjunctive test results, clinicopathologic correlation, and therapy. Participants should also understand the basis for establishing a specific diagnosis of cutaneous lymphoma based on current classification and staging.

Perhaps more often than with any other skin disease, establishing or excluding a de novo diagnosis of cutaneous lymphoma is complicated or difficult, or both. A comprehensive, multidisciplinary evaluation is often facilitated by referral to a tertiary care center.[1]

Scientifically, although our tools for evaluating lymphoid infiltrates have never been more sophisticated, numerous, or available, none is perfect, and no single attribute mandates a specific diagnosis without incorporating all available clinical, pathologic, immunohistochemical, and cytogenetic findings. Even after all available data have been obtained, definitive, specific, and prognostically or therapeutically relevant diagnoses may remain elusive. Reasons for uncertainty may include the inability to exclude concomitant or impending systemic lymphoma, inability to definitively distinguish low-grade lymphomas from reactive infiltrates, and/or lack of experience because of the rarity of some lymphomas.

From the Department of Dermatology, University of Connecticut Health Center.
Reprint requests: Maxwell A. Fung, MD, Department of Dermatology, University of Connecticut Health Center, 263 Farmington Ave, Suite 300, Farmington, CT 06030.

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Underlying and complicating these issues is the constantly expanding knowledge in the field and the varying and conflicting opinions about how to interpret new data, which result in constantly evolving classification systems. Eponyms, acronyms, and abbreviations abound, and terms employed by different classification systems are similar but slightly different, adding to the confusion. In an effort to minimize confusion, a glossary defining commonly used terms is included in the Appendix.

This article reviews the evaluation and management of cutaneous lymphoid infiltrates, focusing on cutaneous lymphoma.

HISTORY AND PHYSICAL EXAMINATION

With the exception of early mycosis fungoides (MF), most cutaneous lymphomas and pseudolymphomas manifest as smooth, tumid, erythematous or violaceous papules, nodules, or plaques and are thus relatively nonspecific in appearance like other dermal or subcutaneous infiltrates. However, solitary or grouped lesions, particularly above the waist, often indicate primary cutaneous lymphoma or pseudolymphoma. In contrast, widespread lesions often indicate preexisting or concomitant systemic lymphoma (secondary cutaneous lymphoma). Some lymphoproliferative disorders have distinctive clinical features. For example, adult T-cell leukemia/lym-

Abbreviations used:

AILD:	angioimmunoblastic lymphadenopathy with dysproteinemia
ALL:	acute lymphoblastic leukemia
ATL:	adult T-cell leukemia/lymphoma
BCL:	B-cell lymphoma
B-LBL:	B-lymphoblastic lymphoma
CBCL:	cutaneous B-cell lymphoma
CLL:	chronic lymphocytic leukemia
CTCL:	cutaneous T-cell lymphoma
EBV:	Epstein-Barr virus
EMA:	epithelial membrane antigen
EORTC:	European Organization for Research and Treatment of Cancer
FCCL:	follicle center cell lymphoma
FCL:	follicle center lymphoma
FDA:	Food and Drug Administration
FL:	follicular lymphoma
GRA:	gene rearrangement analysis
HD:	Hodgkin's disease
HTLV-I:	human T-lymphotropic virus type 1
IFN:	interferon
IL:	interleukin
LBCL:	large B-cell lymphoma
LBL:	lymphoblastic lymphoma
LL:	Lennert's lymphoma
LyP:	lymphomatoid papulosis
MALT:	mucosa-associated lymphoid tissue
MCL:	mantle cell lymphoma
MF:	mycosis fungoides
MZL:	marginal zone lymphoma
NK:	natural killer (cell)
PCR:	polymerase chain reaction
PTL:	pleomorphic T-cell lymphoma
REAL:	Revised European-American Lymphoma (classification)
SLL:	small lymphocytic lymphoma
SPTL:	subcutaneous panniculitis–like T-cell lymphoma
SS:	Sézary syndrome
TCR:	T-cell receptor
T-LBL:	T-lymphoblastic lymphoma
TSEB:	total skin electron beam (therapy)
WHO:	World Health Organization

phoma (ATL) should be suspected in patients from characteristic geographic locations who present with rapidly progressive skin lesions and systemic symptoms, including hypercalcemia. The skin lesions in patch- or plaque-stage MF frequently present with diagnostic clinical morphology and distribution. Chronically recurring, randomly scattered papules that spontaneously involute and histologically resemble MF, large T-cell lymphoma, or Hodgkin's disease (HD) are diagnostic of lymphomatoid papulosis (LyP). In fact, most lymphomas, when studied in large numbers, have characteristic tendencies in relation to appearance, location, or age at onset and are detailed later in this article (Table I). Lymphoproliferative disorders associated with immunosuppression such as AIDS or the posttransplantation setting also represent a unique but diverse subset.

THE INITIAL BIOPSY

For the evaluation of cutaneous lymphoma or pseudolymphoma characterized by dermal papules, nodules, or plaques, the ideal specimen is from an excisional or incisional biopsy and includes subcutis and is part formalin-fixed and, if possible, part fresh/frozen. (Specimens must be handled gently since lymphoid infiltrates are particularly susceptible to crush artifact.) Gene rearrangement analysis (GRA) and an ever-increasing number of immunophenotypic studies can be performed on formalin-fixed tissue, but there remain important markers that are best studied in fresh-frozen tissue, such as those for CD23 and $\alpha\beta$ T-cell receptor (TCR) or $\gamma\delta$ TCR expression. In practice, an initial biopsy specimen will confirm the lymphoid nature of a lesion, and the patient may need a second biopsy, some or all of which may be preserved frozen.

Having stated that, distinguishing early MF from inflammatory disorders is the most common lymphoma setting encountered by dermatologists, and an alternative sampling technique is acceptable. Since the diagnostic features in early MF are superficial, often focal, often subtle, and thus often nondiagnostic, obtaining a long, approximately 1 cm (but not necessarily wide) shave biopsy specimen, sectioned longitudinally, often makes histologic analysis easier and may improve diagnostic precision, which would avoid repeat biopsy. The tissue can be placed flat onto a piece of paper to prevent curling during formalin fixation. Obtaining fresh-frozen tissue for early MF remains the routine at some academic medical centers but is generally not a necessary component of the initial biopsy.

LIGHT MICROSCOPY

Microscopic assessment of formalin-fixed, hematoxylin-eosin–stained tissue sections is a requisite first step in the evaluation of suspected cutaneous lymphoproliferative disorders. Based on the growth pattern and cytologic features, most neoplasms can be classified as lymphoid or nonlymphoid and benign or malignant. However, distinguishing nodular T- or B-cell pseudolymphoma from lymphomas containing small or medium-sized cells, such as marginal zone lymphoma (MZL), is often not possible without further studies.

Table I. Clinical features of cutaneous lymphomas

	Morphology	Spontaneous regression?	Typical distribution	Other features
MF	Patches, P, N, E	Occasionally	Patches: bathing trunk	Many clinical variants
SS	E		Generalized	Keratoderma, lymphadenopathy
Large T-cell lymphoma	P, N, ulcer	Occasionally	Trunk or extremity	Primary: adults; secondary: children, adults
Angiocentric lymphoma	N, ulcer, hydroa-like		Extremities	Found in Asia, Central/South America more often than in North America or Europe; hemophagocytosis
SPTL	P, N		Extremities	Indolent or aggressive with hemophagocytosis
ATL	P, N		Random	HOTS
AILD	P, N, maculopapular, purpura	Occasionally	Maculopapular: trunk; acral petechiae	B symptoms, adenopathy
PTL	P, N		Random	Adults
LL	P, N		Random	Adults
LyP	N, ulcer/papulonecrotic	Always	Random	—
MZL	P, N		Primary: extremity	—
FL	P, N		Primary: head/neck	—
LBCL	P, N		Random; leg	—
CLL	P, N, leonine facies, vesiculobullous	—	Random; sites of old HSV/VZV lesions	—
Plasmacytoma	P, N	—	Random	Secondary: bone pain, paraproteins, amyloidosis, renal failure
MCL	P, N, vegetating surface	—	Random	—
LBL	N	—	Random	Children or adults
HD	P, N	—	Extremity distal to involved lymph node	B symptoms
Intravascular lymphoma	Purpura, patches, P	—	Trunk, extremity	Neurologic symptoms

E, Erythroderma; *HOTS, h*ypercalcemia, *o*steolytic bone lesions, *T*-cell leukemia, *s*plenomegaly; *HSV/VZV,* herpes simplex virus/varicella zoster virus; *N,* papules/nodules; *P,* plaques; for all other abbreviations, see abbreviations box at beginning of article.

Patch- or plaque-stage lesions of MF are usually diagnosed on the basis of light microscopic features and clinical correlation. Histologic criteria for the diagnosis of MF are especially important because, unlike most lymphomas, attempts to strengthen a diagnosis of early MF using immunohistochemistry are frequently inconclusive. In addition, very early MF resembles inflammatory dermatoses. Thus pathologists, dermatologists, and dermatopathologists are at risk for overcalling or undercalling this diagnosis or else cannot render a diagnosis with confidence. In fact, studies document interobserver and intraobserver variability in the diagnosis of early MF even among experts.[2-6]

IMMUNOPHENOTYPING

All suspected cutaneous lymphomas should be evaluated by immunohistochemical studies, commonly referred to as "B and T cell markers" (Tables II and III). Immunohistochemical studies are essential for distinguishing B, T, natural killer (NK), and nonlymphoid cells, identifying subsets of these cells based on their immunophenotype (eg, $CD3^+/CD4^+$ T helper cells [T_H] or $CD3^+/CD8^+$ T cytotoxic/suppressor [T_C] cells), and inferring clonality among B cells that manufacture immunoglobulin as evidenced by κ or λ light-chain restriction. Most reactive, polyclonal infiltrates express a κ/λ ratio of approximately 2:1. Ratios greater than 5-10:1 (κ restriction) or less than 0.5-1:1 (λ restriction) indicate clonality. Flow cytometry studies using fluorescence-activated cell sorter analysis accomplish essentially the same task, although without benefit of correlating the microscopic findings with the immunophenotype. Flow cytometric analysis may provide more objective, quantitative immunophenotyping, but skin specimens are often smaller and not as purely lymphoid as tissue obtained from lymph nodes or bone marrow and are often not amenable to analysis by flow cytom-

Table II. Immunogenetic features in T- and NK-cell lymphomas

		CD2	CD3	CD4	CD5	CD7	CD8	CD30	CD45RO	CD56
MF	Patch	+	+	+ > –	+	+/–	– > +	–	+	–
	Plaque	+	+	+ > –	+	+/–	– > +	–	+	–
	Tumor	+/–	+/–	+ > –	+/–	– > +	– > +	– > +	+/–	–
	Erythrodermic	+	+	+ > –	+	– > +	– > +	–	+	–
	Follicular mucinosis	+	+	+ > –	+	+	– > +	–	+	–
	Pagetoid reticulosis		+	+/–	+	+/–	+/–	+/–	+/–	–
	Granulomatous slack skin		+	+		– > +	–	–		–
SS			+	+	+	+/–	–	–	+	–
Large T-cell lymphoma	$CD30^-$	+/–	+/–	+	+/–		–	–		–
	$CD30^+$	+/–	+/–	+ > –	+/–		–	+		
LyP	Types A, C	+/–	+	+ > –	+/–		–	+		–
	Type B		+	+			–	–		–
Angiocentric lymphoma		+	+/–	+/–	+/–	+/–	+/–			+/–
SPTL			+	+/–	+/–	+/–	+/–			– > +
ATL		+	+	+ > –	+	–	– > +			–
AILD			+	+						–
PTL		+/–	+ > –	+ > –	+ > –	–	– > +	– > +		– > +
T-LBL		+ > –	+	+/–	+/–	+	+/–		+	–
CLL		+/–	+	+ > –	+/–	+	– > +			–

+, Positive; –, negative; *ALK,* anaplastic lymphoma kinase; *TdT,* terminal deoxynucleotidyl transferase; for all other abbreviations see the abbreviations box at beginning of article.

Table III. Immunogenetic features in CBCL and HD

		CD5	CD10	CD19	CD20	CD21	CD23	CD30	CD43	CD79a
MZL		–	– > +	+	+ > –		– > +		+/–	+
Immunocytoma		–	–	+	+ > –		–		+/–	
FL/FCCL		–	–	+	+		– > +		–	+
LBCL		– > +	– > +	+	+			–		+
CLL/SLL		+ (f), +/–(p)	–	+	+		+		+	+
Plasmacytoma				–	–			+/–	+/–	+/–
MCL		+	–	+	+	+	–		+	
B-LBL		–	+	+	– > +					+
HD	Lymphocyte-predominant			+	+			+/–		+
	Nodular sclerosing			–	–			+		–
	Mixed cellularity			– > +	– > +			+		– > +
	Lymphocyte-depleted			–	–			+		–
Intravascular lymphoma				+	+					+

f, Frozen tissue; *p,* paraffin-embedded, formalin-fixed tissue; for all other abbreviations, see abbreviations box at beginning of article.

etry. Fluorescence-activated cell sorter analysis of peripheral blood samples is effective.

GENE REARRANGEMENT ANALYSIS

As lymphocytes differentiate into B and T cells from undifferentiated thymocytes, certain genes are rearranged in a manner characteristic for each single lymphocyte (ie, immunoglobulin genes in B cells and TCR genes in T cells).[7] Because clonal proliferation originating from a single lymphocyte is a constant feature of malignancy, populations of neoplastic lymphocytes contain the same "signature" gene

Lesional GRA	Other
+/–	
+	
+	
+	Sézary cell count +/–
+	
+	
+	
+	Sézary cell count +
+	
+	ALK +/–, t(2;5)
+ > –	$CD15^-$/EMA^-
+ > –	
+ (T-cell), – (NK-cell)	EBV^+ if $CD56^+$
+/–	
+	HTLV-I, $CD25^+$ blood
+	
+ > –	
+/–	TdT^+; $CD4^+CD8^+$ or $CD4^-CD8^-$; usually B cell in skin
+	Usually B cell

$_cIg$	$_sIg$	Lesional GRA	Other
+/–	+/–	+	Trisomy 3
+	+/–	+	
–	+	+	
+/–	+/–	+	
– > +	+	+	Trisomy 12, *bcl*-1^+
+	–	+	$CD45^-$, $EMA^{+/-}$
–	+	+	*bcl*-1^+
+/–	–	+/–	TdT^+
–	–	–	$CD15^-$
		– > +	$CD15^+$
		–	$CD15^+$
		–	$CD15^+$
	+	+	

rearrangement, whereas most populations of reactive lymphocytes contain a mixture of gene rearrangements. This difference can be detected using GRA of DNA extracted from a tissue specimen. NK cells are not antigen-specific and do not undergo a known characteristic gene rearrangement.

The Southern blot technique requires DNA extracted from fresh-frozen tissue and has a sensitivity range of 1% to 5%, meaning that a clonal population comprising as little as 1% to 5% of the cells in the specimen can be identified. This level of sensitivity is usually sufficient for analysis of peripheral blood, lymph nodes, and dense lymphoid infiltrates in other tissues including skin. The technique can also be used to identify integration of viral genomes, such as HTLV-I in the neoplastic lymphocytes of ATL. Drawbacks of the Southern blot technique include the requirement for fresh tissue and the inability to reliably detect gene rearrangements in sparse infiltrates below the sensitivity of the technique.

The techniques of polymerase chain reaction (PCR) employ nucleotide primers to locate and amplify specific DNA segments from tissue and have a sensitivity range of 0.001% to 1%, up to 1000 times more sensitive than Southern blot. A second advantage of PCR is the ability to utilize DNA extracted from unstained sections of archived, formalin-fixed tissue. Fresh-frozen tissue also works but is not necessarily better. PCR-based methods have become the standard for evaluating cutaneous lymphoid infiltrates.[8]

As with immunophenotyping, results of GRA by either method should always be interpreted in the clinical context. False-negative and false-positive results may occur depending on several factors including sample size, sample characteristics, sampling error, and other technical factors or limitations. For example, PCR-GRA requires the use of multiple primers that recognize critical segments of the rearranged TCR β- or γ-chain genes or the rearranged heavy and light chains of immunoglobulin genes. Unfortunately, even the most comprehensive sets of available primers are not complete and thus cannot detect all possible rearrangements. Furthermore, rearranged genes may be deleted or undergo somatic mutation (resulting in suboptimal primer binding). Despite the fact that most T cells and T-cell lymphomas express TCR α/β, TCR γ-chain genes contain fewer variable (V) and junctional (J) gene segments and are rearranged earlier (and more frequently) in T-cell lymphomas than TCR β genes. Therefore GRA for rearranged TCR γ-chain genes is currently the simplest and best single study. PCR-GRA can be used to monitor the response of CTCL to therapy and detect minimal residual disease. Clinical responses are correlated with the presence or absence of the malignant clone in the skin or blood. Like immunohistochemistry, protocols for PCR are variable and optimized in the laboratories that perform them.

Critically important is the recognition that although clonality is a hallmark of malignancy, not all clonal proliferations are malignant. Examples of clin-

Table IV. TNMB classification system for CTCL[155,245]

T	T0	Nondiagnostic (eg, "parapsoriasis")
	T1	Limited patch/plaque (<10% total skin surface)
	T2	Generalized patch/plaque (≥10% total skin surface)
	T3	Tumors
	T4	Erythroderma
N	N0	Lymph nodes clinically uninvolved
	N1	Lymph nodes enlarged, histologically uninvolved (eg, dermatopathic)
	N2	Lymph nodes clinically uninvolved, histologically involved
	N3	Lymph nodes enlarged and histologically involved
M	M0	No visceral involvement
	M1	Visceral involvement
B	B0	Circulating atypical/Sézary cells (<5% of lymphocytes)
	B1	Circulating atypical/Sézary cells (≥5% of lymphocytes)

Table V. Clinical staging for CTCL[17,155,245]

Stage	T	N	M
IA	1	0	0
IB	2	0	0
IIA	1-2	1	0
IIB	3	0-1	0
III	4	0 (A); 1(B)	0
IVA	1-4	2-3	0
IVB	1-4	0-3	1

ically benign diseases that sometimes demonstrate clonal TCR gene rearrangement include LyP, lichen planus, pityriasis lichenoides, pigmented purpura, and lichen sclerosus.[9] The term *clonal dermatitis* has been suggested for histologically benign dermatoses that demonstrate clonal bands. These dermatoses may be the precursors of CTCL or may already be CTCL, without diagnostic histologic findings.[10] This raises the important issue of the balance between the sensitivity and specificity of PCR assays in the differential diagnosis of benign cutaneous lymphoid infiltrates and cutaneous lymphoma. The estimated maximal T-cell clonal density in "true" inflammatory lesions such as allergic contact dermatitis is 0.1%.[11] Therefore the optimal diagnostically relevant sensitivity may be less than the maximal sensitivity of PCR-based assays, in the range of 0.1% to 1.0%.

STAGING

With respect to cutaneous lymphoma, it is critical to recognize whether the lymphoma is a primary cutaneous lymphoma or has arisen in association with a nodal or extranodal systemic lymphoma (secondary cutaneous). The prognosis is invariably worse in secondary compared with primary cutaneous lymphoma, irrespective of the histologic diagnosis. The early stages of MF are generally assumed to be primary cutaneous. The European Organization for Research and Treatment of Cancer (EORTC) has proposed a working definition requiring a negative systemic evaluation at baseline and at 6 months before establishing a diagnosis of primary cutaneous lymphoma.[12] Explicit guidelines for the evaluation and longitudinal management of patients with cutaneous lymphoma have not been formally established, but a baseline work-up should include complete physical examination with attention to lymphadenopathy and hepatosplenomegaly, and, with the possible exception of early (stage I) MF, peripheral blood analysis (complete blood cell count with manual differential, Sézary cell count, flow cytometry, and/or GRA), and computed tomographic scanning of the chest, abdomen, and pelvis. Bone marrow involvement in MF is uncommon except in advanced disease. However, patients with CTCL expressing a cytotoxic phenotype (CD8, TIA-1, granzyme), TCR γδ, all NK, and all B-cell lymphomas should be considered for bone marrow biopsy. The potential role of sentinel lymph nodectomy in cutaneous large B-cell lymphomas (LBCLs) confined to the extremities has been reported.[13] In all forms of cutaneous lymphoma, even after complete remission has been achieved, indefinite follow-up is indicated.

The TNMB (*t*umor, *n*ode, *m*etastasis, *b*lood) classification system (Table IV) defines the clinical stage in CTCL (Table V). Since chronic patches and plaques of CTCL are generally assumed to represent primary CTCL, namely MF, patients are often classified as having T1 (stage Ia), T2 (stage Ib), T3 (tumors, stage IIb) or T4 (erythroderma, stage III) disease. The determination of whether lesions represent patches or plaques should include both clinical and histopathologic criteria.

In cutaneous B-cell lymphoma (CBCL), involvement is considered either primary cutaneous or secondary to spread from an extracutaneous site such as a lymph node– or mucosa-associated lymphoid tissue (MALT). The term *secondary cutaneous lymphoma* is less commonly used to designate transformation of low-grade cutaneous lymphoma into high-grade lymphoma but, to avoid confusion, has not been encouraged.[14]

CLASSIFICATION

Modern lymphoma classifications attempt to recognize discrete clinicopathologic entities based on both clinical features and identification of the neoplastic cell type based on resemblance to its postu-

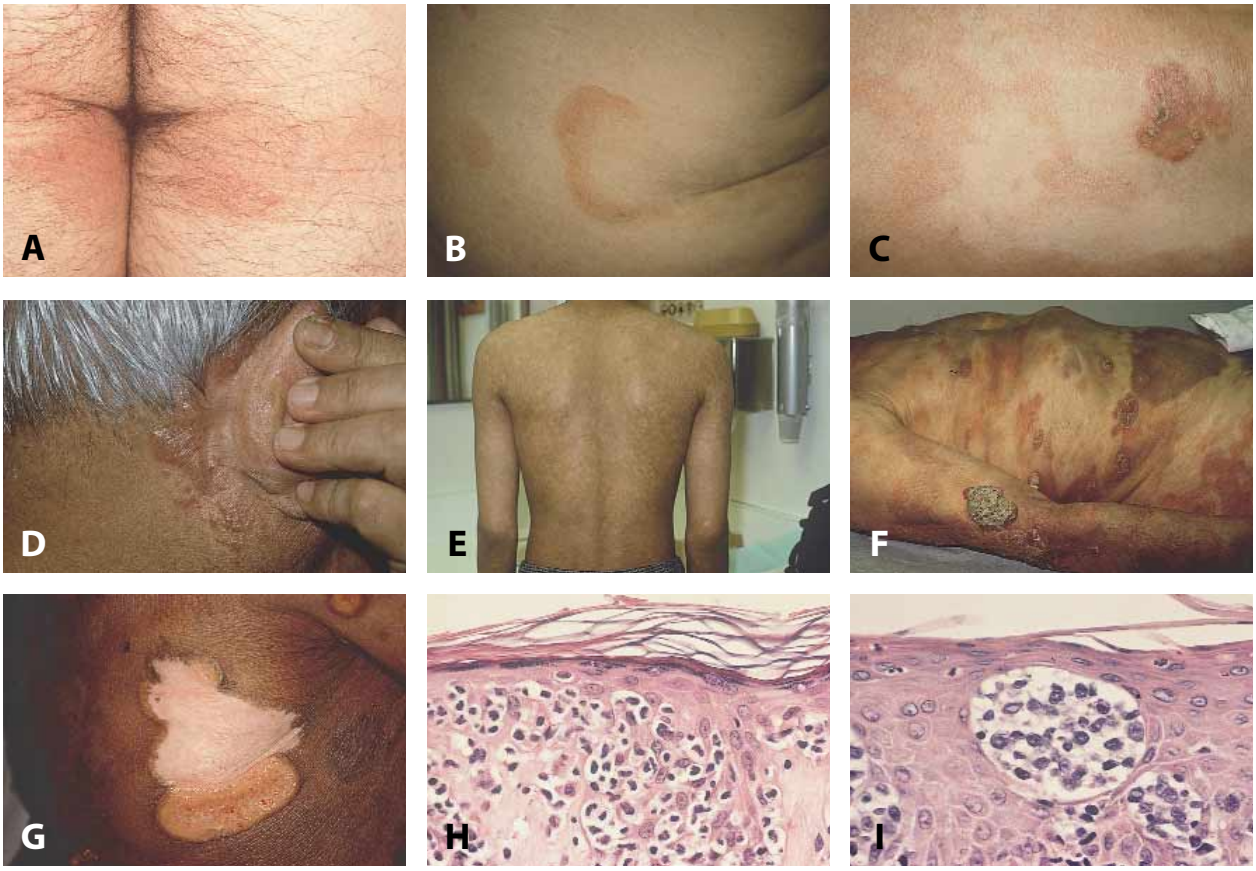

Fig 1. MF. **A-C,** Patches and plaques of MF. **D,** Follicular mucinosis in patient with MF. **E,** Hypopigmented variant of generalized patch-stage (T2) MF. **F,** Tumors of MF arising in association with patches and plaques. **G,** Ulcerative plaques. **H,** Epidermotropism is characteristic in patches, plaques, and erythroderma. **I,** Pautrier's microabscesses. This patient was erythrodermic.

lated physiologic counterpart. Other designations such as angiocentric, subcutaneous panniculitis-like, or intravascular lymphoma are defined by their growth pattern and may have variable immunogenetic features. These may require further reclassification in the future.

Several lymphoma classifications have been proposed, and more revisions are on the way. Earlier efforts such as the Kiel, Rappaport, and Lukes and Collins classifications were based on morphologic features of systemic lymphomas and did not account for clinical features, immunophenotypic and cytogenetic characteristics, or particular aspects of cutaneous lymphomas. The 1994 Revised European-American Lymphoma (REAL) classification of the International Lymphoma Study Group was the first to incorporate clinical, histologic, immunophenotypic, and molecular genetic information.[15] The most recent classification of the World Health Organization (WHO) follows the same principles and is the most current and comprehensive classification.[16] Developing in parallel, however, was the increasing recognition that primary cutaneous lymphomas invariably carry a better prognosis compared with systemic lymphomas that are otherwise histologically and immunophenotypically identical. This concept is highlighted in the 1997 Primary Cutaneous Lymphoma classification of the EORTC,[12] which does not address lymphomas that present with secondary cutaneous lesions and was not based on an international consensus group, but represents the most comprehensive classification devoted to cutaneous lymphoma. The following discussion includes most cutaneous lymphomas, primary or secondary, included in the EORTC, REAL, and/or WHO classifications.[17]

CUTANEOUS T-CELL LYMPHOMAS: CHARACTERISTICS

Mycosis fungoides (Fig 1)

MF is classified as an indolent lymphoma by the EORTC. The postulated normal counterpart is the

recirculating epidermotropic $CD4^+$ T cell. The prognosis for patch-stage or limited plaques, which includes most cases, is similar to that for normal age-matched control subjects.[18-20] In contrast, 5-year survival for tumor and erythrodermic stages decreases to approximately 40%.[21] Like most other lymphomas, the cause is unknown; however, HTLV-I may play a role in some cases.[22] This theory is controversial.[23] Patients with industrial occupations have been reported to have a relatively higher risk of acquiring MF as well as decreased survival,[24] although modifiable risk factors were not identified in the largest case control study to date.[25]

Classically, MF is typified by the gradual progression from patches (flat, scaly, various shades of red, variably pruritic) and plaques (indurated, often annular with central clearing), mostly on photoprotected sites, to tumors. However, most patients with patches or plaques never have disease progression to tumor or erythrodermic stages, in contrast to Alibert's original description of the disease in 1846. Erythroderma may intervene at any time, and its distinction from Sézary syndrome (SS) depends on the findings in peripheral blood and other clinical features (see the section on SS). In fact, MF may present at any stage and unusual clinical and histopathologic variants often coexist with typical patches or plaques. Clinical variants include pagetoid reticulosis, follicular mucinosis with or without alopecia (alopecia mucinosis), hypopigmented MF, and granulomatous slack skin. Rarely, pityriasis lichenoides–like,[26] verrucous, purpuric,[27] pustular, or bullous lesions have been described.[28] Leukoderma (depigmentation) is uncommonly associated with erythroderma.[29] The common denominator among all variants is the presence of diagnostic histologic findings.

Microscopically, patch-stage MF exhibits a sparse papillary dermal lymphocytic infiltrate with epidermotropism, in which small to medium-sized lymphocytes aggregate usually within the lower half of the epidermis near the basal layer. Compared with spongiotic (eczematous) dermatitis, associated spongiosis is usually absent or disproportionately minimal. Hyperchromatic, convoluted, or cerebriform nuclei may not be apparent, though there may be conspicuous halos caused by retraction artifact surrounding intraepidermal lymphocytes, and those lymphocytes may have slightly larger nuclei, on average, than those in the dermis. Atypical lymphocytes, either in collections (Pautrier's microabscesses) or singly within the epidermis, are probably the most specific finding in early MF but are infrequently present in the earliest patches.[30-33] Variable findings include presence of exocytosis (defined here as the presence of lymphocytes in the epidermis, randomly scattered at all levels of the epidermis, and usually associated with spongiosis),[34] necrotic keratinocytes, vacuolar alteration,[35] psoriasiform epidermal hyperplasia, papillary dermal fibrosis, dermal eosinophils and plasma cells, orthokeratosis, focal parakeratosis, and atrophy/effacement of rete ridges with dermal melanophages typical of poikilodermatous MF. Skin biopsy specimens may prove nondiagnostic, and longitudinal observation and repeat biopsy may be required to establish a definitive diagnosis. Rather than relying on any single criterion, the histologic diagnosis depends on integrating a constellation of parameters.[36] Plaques of MF, in contrast, are usually diagnostic, exhibiting all of the findings of patches, and more, including (1) deeper and denser dermal infiltrates, producing a lichenoid pattern at scanning magnification, often with perivascular or diffuse infiltrates in the reticular dermis; (2) cytologically atypical intraepidermal lymphocytes; (3) easily found Pautrier's microabscesses; and (4) more prominent psoriasiform hyperplasia and papillary dermal fibrosis. Follicular mucinosis may be seen, characterized by folliculotropism and often numerous eosinophils and plasma cells. In the granulomatous variant, nodular, palisaded, or interstitial granulomatous infiltrates may obscure the neoplastic nature of MF. Except for the presence of overlying epidermotropism, the lesions may resemble those of Lennert's (lymphoepithelioid) lymphoma (LL), a systemic T-cell lymphoma that involves skin in only 10% of cases.

Other notable histologic features that may be seen in MF include spongiotic vesiculation, dermal mucin, predominantly dermal infiltrates (usually associated with concurrent therapy), adnexotropic (eccrine gland and hair follicle) infiltrates,[37] syringolymphoid hyperplasia, verrucous hyperkeratosis, pustules, subepidermal or intraepidermal bullae, angiocentricity, acanthosis nigricans–like epidermal hyperplasia, or superimposed lichen simplex chronicus.[28] Atypical changes reminiscent of those associated with systemic chemotherapy, including atypical keratinocytes, vacuolar interface dermatitis, plump atypical endothelial cells, and atypical fibroblasts have been reported in patients being treated with topical nitrogen mustard.[38] Tumors contain nodular or diffuse proliferations of small, medium-sized, and sometimes large atypical lymphocytes. Large lymphocytes in small nodules or comprising more than 25% of the total infiltrate indicates transformation, characteristically a sign of poor prognosis. Transformation is a common feature in tumors of MF.[39] Epidermotropism is frequently diminished, so the differential diagnosis may initially include CBCL. Erythrodermic MF may be histologically indistin-

guishable from patch-stage MF. Unfortunately, the critical features are often even more subtle, so nondiagnostic biopsies are more common.[40] Pagetoid reticulosis exhibits prominent epidermotropism with clustered medium-sized and large atypical lymphocytes with hyperchromatic cerebriform nuclei, clear pericellular halos, and abundant vacuolated cytoplasm in pagetoid array within an acanthotic epidermis. The pendulous lesions in granulomatous slack skin show a marked expansion of the reticular dermis containing small atypical lymphocytes and characteristic multinucleated histiocytes that often contain numerous nuclei, often in a wreath-like array, and some with lymphophagocytosis. There is elastophagocytosis and a marked decrease in dermal elastic tissue. Early lesions are similar to classic patch-stage MF. MF cells variably express T-cell markers (CD2, CD3, CD5, CD7, Leu-8, CD45RO), the hallmark being the T helper/inducer subset marker, CD4. Rare cases are $CD4^-/CD8^+$ (cytotoxic/suppressor subset) and may correlate with a more aggressive clinical phenotype.[41-43] The T cells in many cases of pagetoid reticulosis express a cytotoxic/suppressor phenotype, suggesting that at least some examples may represent a distinct subset of CTCL.[44-48] Deletion of CD7 (Leu-9) or Leu-8 is present in approximately 50% to 75% of cases, usually tumors, but these deletions are also present in more than 40% of nonlymphoma controls.[49] However, CD7 deletion becomes more specific for MF if a lower percentage of positive cells is used as the cutoff.[50-52] CD25 (interleukin 2 [IL-2] receptor) is expressed in a minority of cases. Rarely, intraepidermal lymphocytes may express CD30.[53] Clonal rearrangement of TCR genes can be demonstrated in lesional tissue in most cases, including pagetoid reticulosis, follicular mucinosis, and granulomatous slack skin, and at least 50% of patch-stage lesions by PCR-based methods.[54] Mutations of the $p16^{INK4a}$ tumor suppressor gene have been detected in MF.[55] Flow cytometry may detect aneuploidy in a minority of early cases.[56]

Although more common in adults, the occurrence of MF in children is well documented.[57-61] Children and adults younger than 35 years tend to present with early-stage disease, with no apparent difference in prognosis.[60]

Sézary syndrome

SS is classified by the EORTC as an aggressive lymphoma. Some consider SS to be a variant within the spectrum of MF, but the estimated 5-year survival rate in SS is 11%.[12] The historical SS triad includes erythroderma, lymphadenopathy, and cerebriform lymphocytes (Sézary cells) in the peripheral blood, lymph nodes, and skin. Today, peripheral blood and lesional immunophenotyping and gene rearrangement studies supplement and, in some institutions, replace the more variable and subjective Sézary cell count. Thus, in the appropriate clinical context, evidence supporting a diagnosis of SS includes Sézary cells comprising more than 5% to 20% of circulating lymphocytes or more than $1000/mm^3$, an expanded population of $CD4^+/CD7^-$ circulating lymphocytes by flow cytometry,[62] an elevated CD4/CD8 ratio,[63] or a clonal TCR gene rearrangement. As in MF, the postulated normal counterpart is the recirculating epidermotropic $CD4^+$ T cell. Pruritus, erythroderma, keratoderma, alopecia, lymphadenopathy, and splenomegaly characterize SS. Patients with SS may also have patches, plaques, and tumors, which are clinically and histologically indistinguishable from those in MF. Histologicaly, SS is indistinguishable from patch-stage and erythrodermic MF, although the histologic features are often extremely subtle. SS may also be associated with lymphopenia that may correlate with an increased incidence of secondary malignancy including squamous cell carcinoma of the skin or oral mucosa, or HD.[64,65]

Large T-cell lymphoma, $CD30^+/CD30^-$

Termed anaplastic large-cell lymphoma in the REAL classification, EORTC dropped the "anaplastic" from these histologically distinctive lymphomas because not every such tumor histologically exhibits anaplastic cells.[66] Other designations include large-cell anaplastic lymphoma and regressing atypical histiocytosis.[67] The postulated normal counterpart is a $CD30^+$ (or $CD30^-$) extrafollicular blast. $CD30^+$ large T-cell lymphoma may be the most common form of non-MF primary CTCL,[68] although in one recent series, pleomorphic T-cell lymphoma (PTL) slightly outnumbered anaplastic large-cell lymphoma.[69] $CD30^-$ lymphomas with similar histologic features appear to have an entirely different natural history. Thus a critical distinction is whether the large cells label with CD30 (Ki-1), since primary cutaneous $CD30^+$ large-cell lymphomas are relatively indolent neoplasms with estimated 5-year survival of up to 90%, whereas otherwise indistinguishable primary cutaneous $CD30^-$ lymphomas are aggressive neoplasms, with an abysmal 15% 5-year survival in the same registry.[12] One report suggests that prompt induction of clinical remission may not affect this prognosis.[70] Primary cutaneous examples usually appear as a solitary or localized nodule (Fig 2), often ulcerating, usually on the extremity[71] or trunk of an adult. Up to 25% of these patients may experience complete or partial spontaneous regression. The differential diagnosis may include pyoderma gangrenosum.[72] Primary cutaneous $CD30^+$ lesions occur in

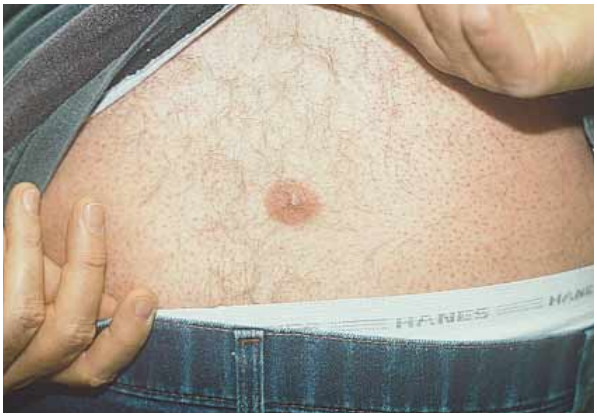

Fig 2. A 53-year-old man with primary cutaneous CD30+ large (anaplastic) T-cell lymphoma on the lower back.

adults but are rare in children,[73] whereas systemic CD30+ lymphomas occur bimodally in children and adults. Expression of anaplastic lymphoma kinase is associated with a t(2;5) translocation and is a favorable prognostic factor in systemic CD30+ large T-cell lymphomas that may involve the skin. Anaplastic lymphoma kinase expression is rare in LyP and primary cutaneous large T- or NK cell lymphoma.[74-76] In large T-cell lymphomas (CD30+ or CD30–), there is usually a diffuse, nonepidermotropic, sheetlike pattern of growth, often with overlying ulceration, epidermal hyperplasia, and neutrophilic infiltrates. Many of the large cells possess anaplastic nuclear features, consisting of large, irregularly and variably shaped hyperchromatic or vesicular nuclei with one or more prominent eosinophilic nucleoli (reminiscent of those seen in the Reed-Sternberg cell of HD) and abundant slightly basophilic cytoplasm. Anaplastic cells often have kidney-shaped, horseshoe-shaped, U-shaped, or embryo-shaped nuclei and may be multinucleate (termed "donut cells" when in wreath-like array). Anaplastic cells are usually larger than immunoblasts or centroblasts, which themselves are classified as large and are typically present. Overall, large cells comprise at least 30% of the cellular infiltrate with at least 75% of large cells reactive for CD30+ in a membranous and paranuclear pattern. There is sometimes an admixture of small lymphocytes, histiocytes, neutrophils, and eosinophils, creating a resemblance to LyP. Rare CD30/CD56 coexpression has been reported and may correlate with aggressive biologic behavior.[77,78] However, expression of a TIA-1+/granzyme B+ cytotoxic phenotype is relatively common and does not appear to correlate with aggressive behavior.[79] In contrast to systemic lymphomas, CD15 and epithelial membrane antigen (EMA) are usually negative and cutaneous lymphocyte antigen is positive in primary cutaneous examples. Clonal TCR gene rearrangements are present. Benign, self-limited eruptions containing predominantly large CD30+ large atypical cells have also been described in association with chemotherapy for non–T-cell hematolymphoid malignancies. These eruptions have exhibited a superficial perivascular pattern of infiltrate, but clinical correlation and follow-up are essential.[80]

Lymphomatoid papulosis

LyP is included in most discussions of CTCL because of its associations with and histologic resemblance to lymphoma, and it is positioned at the benign end of a spectrum of CD30+ lymphoproliferative disorders with CD30+ large T-cell lymphoma.[81] It is classified as an indolent form of CTCL by EORTC and survival approximates 100%. Rare cases that have been diagnosed histologically as primary cutaneous HD, pseudo-HD, or lymphomatoid pityriasis lichenoides could be classified as LyP.[82,83] "Rhythmic paradoxical eruptions" are also united under this heading.[84] Clinically, LyP is characterized by randomly scattered, occasionally pruritic papules and nodules, often crusted or necrotic, in various stages of evolution, which spontaneously regress usually within 1 to 2 months, leaving scars and dyspigmentation. The condition runs a chronic course lasting months to decades, mostly frequently involving the trunk, buttock, and extremities. In approximately 25% of cases diagnosed in referral centers, LyP is associated with MF/SS.[69] Most cases of MF precede the diagnosis of LyP, but associations may also occur concurrently or subsequently.[85] CD30+ large T-cell lymphoma, HD, and other lymphomas have also been associated with LyP.[86] LyP may occur at any age but most commonly arises in the fourth or fifth decade of life.[71,86] Three histologic subtypes are united under the clinical phenotype of LyP. Type A lesions exhibit a dense wedge-shaped mixed inflammatory infiltrate with neutrophils, eosinophils, histiocytes, small lymphocytes, frequent mitotic figures, and clustered or scattered large atypical cells resembling the anaplastic cells of large T-cell lymphoma or Reed-Sternberg cells. Eosinophilic histiocytosis may represent a variant of type A LyP.[87] Occasionally, there is associated vasculitis with atypical mononuclear cells in venules or increased dermal mucin deposition. Overlying atypical epithelial proliferations have been reported as pseudocarcinomatous hyperplasia[88] or keratoacanthoma.[89] Early and waning type A lesions may have few large atypical cells.[90] The differential diagnosis may include pityriasis lichenoides or an arthropod bite reaction. Type B

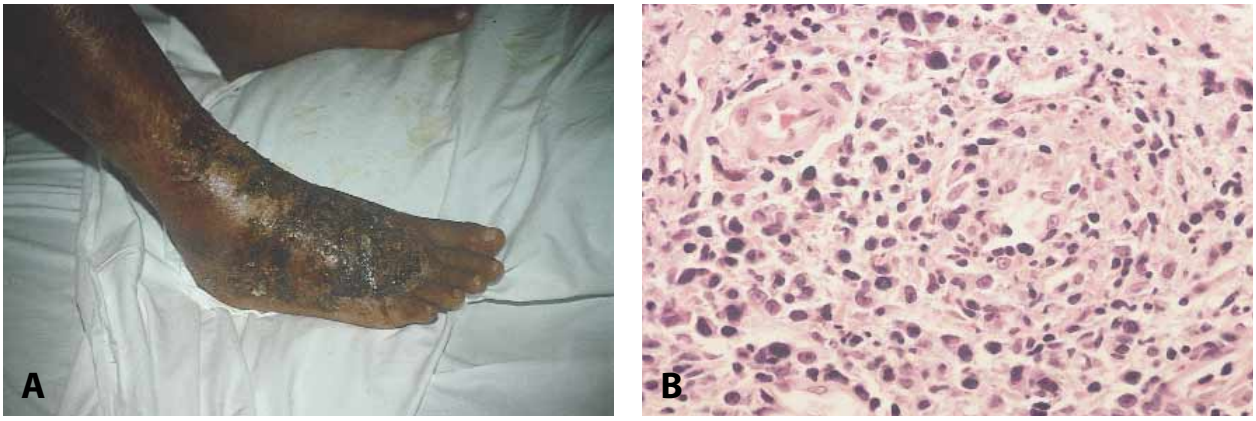

Fig 3. Angiocentric lymphoma. **A,** Crusted, ulcerated plaques. **B,** Atypical lymphocytes disrupt vessel walls.

lesions exhibit a bandlike or nodular monomorphous infiltrate containing small and medium-sized lymphocytes with cerebriform nuclei and epidermotropism resembling a plaque of MF. Large $CD30^+$ cells are not present, and eosinophils and neutrophils are rare. The differential diagnosis may include patch- or plaque-stage MF. Some lesions show a mixture of type A and type B patterns or different patterns in concurrent lesions. A follicular pattern has also been described. Type C lesions contain large clusters or aggregates of large atypical $CD30^+$ cells with few admixed inflammatory cells, similar to large T-cell lymphoma. In fact, the atypical cells in type A and type C lesions are immunophenotypically identical to those in $CD30^+$ large T-cell lymphoma. Clonal TCR gene rearrangement is detected in approximately 60% of cases.

Angiocentric lymphoma

Classified in the REAL classification as nasal-type extranodal NK/T-cell lymphoma, angiocentric lymphoma is a systemic lymphoma with frequent skin manifestations related to its angiodestructive nature. Many cases previously classified as lymphomatoid granulomatosis, lethal midline granuloma, or angiocentric immunoproliferative lesion could be included here, although currently the term *lymphomatoid granulomatosis* should be reserved for B-cell lymphomas involving primarily the lung but sometimes other sites, including skin. The prognosis varies from indolent to aggressive, correlating with the proportion of large cells making up the infiltrate, which in turn may directly correlate with expression of an NK phenotype and clonal integration with Epstein-Barr virus (EBV). The overal 5-year survival is less than 50%.[91] The physiologic counterpart is unknown, presumably a peripheral NK or T-cell subset. Angiocentric lymphoma is uncommon in the United States and Europe and more common in Asia. Cases resembling hydroa vacciniforme in children have been reported in Mexico and Bolivia.[92] Clinically, angiocentric lymphoma presents as dermal or subcutaneous papules or nodules that may ulcerate (Fig 3). Lesions are usually widespread and frequently involve the lower extremities. Pulmonary, neurologic, hemophagocytic, and other systemic symptoms may precede or follow the cutaneous presentation. In hydroa-like angiocentric lymphoma, there are papulovesicles and necrotic scars on the face and extremities.[92]

Microscopically, angiocentric lymphoma exhibits neoplastic lymphocytes within and around the walls of small and medium-sized vessels of the dermis and subcutis associated with zonal tissue necrosis and evidence of vascular damage, namely fibrin deposits, thrombosis, and fibrosis in and around vessel walls with occasional extension into the subcutis.[93] The number of neoplastic lymphocytes may be small, mimicking a reactive infiltrate, particularly when cytologic atypia is minimal. Infiltrates may be monomorphous or variably composed of small, medium-sized, and large lymphocytes with round or irregularly shaped borders and pale cytoplasm. Cerebriform nuclei are uncommon, although the presence of epidermotropism is variable. Ultrastructurally, cells with NK features contain cytoplasmic granules. These may be appreciated on Wright or Giemsa preparations. Eosinophils, plasma cells, and histiocytes are variably present. Angiocentric lymphomas display a spectrum of immunophenotypes, ranging from a T-cell phenotype with variable expression of CD2, CD3, CD4, CD5, CD7, or CD8 on one hand, to an NK ($CD2^+/CD3\varepsilon^+/CD56^+$) phenotype with variable expression of other NK markers,

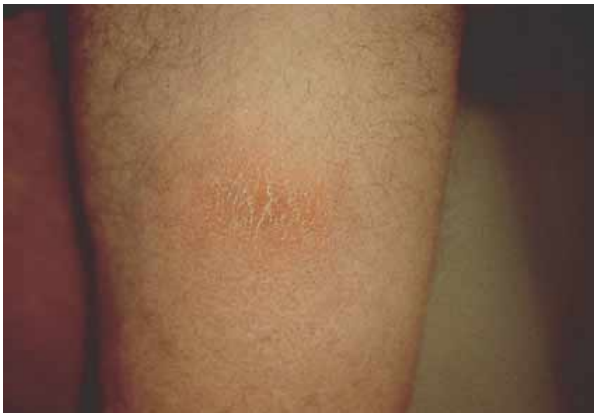

Fig 4. SPTL. (Courtesy of George J. Murakawa, MD, PhD, Detroit, Mich.)

CD16 or CD57. Cases with an intermediate phenotype are termed "NK-like" or "T-NK-like" and may represent a distinct entity with a propensity for bone marrow involvement.[94] Angiocentric NK lymphoma cells usually contain clonally integrated EBV,[95] detectable by immunohistochemistry or in situ hybridization. Angiocentric T-cell lymphomas may also contain EBV. Variable CD30 labeling has been reported in some cases, including those with NK phenotype.[78,79,92,96] TCR gene rearrangement studies are germline (negative) in NK phenotypes but clonal in T and T-NK cases.

Subcutaneous panniculitis–like T-cell lymphoma

Subcutaneous panniculitis–like T-cell lymphoma (SPTL) occurs worldwide and may overlap clinically and histologically with angiocentric lymphoma.[96a] SPTL may evolve from cases initially classified as cytophagic histiocytic panniculitis[97,98] and presumably represents at least some cases that have been previously classified as Weber-Christian disease and fatal panniculitis. The prognosis is poor despite aggressive chemotherapy, with a median survival of less than 3 years.[68] However, a subset of patients follow a chronic, indolent course. The physiologic counterpart is an unknown peripheral T- or NK-cell subset. SPTL presents with subcutaneous nodules and plaques on the legs and less commonly on the trunk, often in young adults (Fig 4).[68,99] Weight loss, fever, and fatigue frequently herald the onset of a rapidly progressive hemophagocytic syndrome, the major cause of death in these persons. Dissemination of lymphoma to extracutaneous sites of hemophagocytosis is uncommon.[99,100] Microscopically, there are septal and lobular infiltrates in the panniculus with zonal tissue necrosis and sometimes angiocentric infiltrates. Often a characteristic rimming of neoplastic cells around individual adipocytes can be observed. The neoplastic cells resemble those seen in PTLs or node-based peripheral T-cell lymphomas with smaller cells displaying hyperchromatic, irregular nuclei and inconspicuous nucleoli, and occasional large anaplastic cells in varying proportions. In some cases, the neoplastic T cells resemble histiocytes, and some authorities believe that some cases of malignant histiocytosis represent SPTL.[100] In addition, when small lymphocytes predominate in SPTL lesions, the neoplastic nature of the lesion may be missed altogether, and the differential diagnosis includes reactive processes such as lupus profundus. There is a variable histiocytic component and occasionally erythrophagocytosis and/or lymphophagocytosis, resulting in "bean-bag cells," correlating with the hemophagocytic syndrome clinically. Nuclear debris, fat necrosis, and granulomatous inflammation are variable findings. Neoplastic lymphocytes are usually $CD4^+$ or $CD8^+$ and may lack CD5 or CD7. CD30 expression is variable.[99] Some cases express CD56, multiple-drug resistance phenotype, and/or contain EBV genome.[101] Clonal TCR gene rearrangements are present. A subset expressing γ/δ TCR may have a poorer prognosis.[102,103]

Adult T-cell leukemia/lymphoma

ATL is induced by infection with human T-cell lymphotropic virus type 1 (HTLV-I), which is endemic to southern Japan, Southeast Asia, the Caribbean, Latin America, equatorial Africa and is more common in recreational intravenous drug users. Only a fraction of infected persons will develop ATL. (HTLV-I is also implicated in tropical spastic paraparesis and infective dermatitis.) ATL is a systemic lymphoma with a median survival of less than 1 year. The postulated normal counterpart is a peripheral $CD4^+$ T cell in various stages of transformation. Typically, there is an acute onset to ATL with leukocytosis, lymphadenopathy, and a characteristic clinical presentation bearing the acronym HOTS (*h*ypercalcemia, *o*steolytic bone lesions, *T*-cell leukemia, *s*plenomegaly). Plaques and nodules resemble those of MF, but patches are rare. Chronic (milder symptoms, slightly longer survival) and "smoldering" (peripheral lymphocytosis only) forms have also been described. The transition to the acute form is termed "crisis."[104] Serum anti-HTLV-I antibodies have been negative in otherwise classic cases.[105] Southern blot technique detects clonal integration of HTLV-I genome within lesional or circulating neoplastic cells.

Papular lesions in ATL contain dense, lichenoid infiltrates of medium-sized lymphocytes with convoluted nuclei. Epidermotropism and periadnexal and

perivascular extension are variable features. Nodules also contain larger lymphocytes with vesicular nuclei resembling histiocytes, the anaplastic cells in large-cell lymphomas, or Reed-Sternberg cells. The peripheral blood contains multilobated (rather than cerebriform) lymphocytes with a classic "cloverleaf" or "flower" appearance. ATL cells are usually $CD3^+/CD4^+/CD7^-$. CD8 expression is rare. CD25 (IL-2 receptor) is expressed on the circulating cells. Clonal TCR gene rearrangements are present.

Angioimmunoblastic T-cell lymphoma

Also known as angioimmunoblastic lymphadenopathy with dysproteinemia (AILD), angioimmunoblastic T-cell lymphoma is a rare, moderately aggressive systemic lymphoma previously regarded as reactive in light of its occasional spontaneous remission and/or apparent response to corticosteroid therapy. In fact, some authorities continue to distinguish AILD as a reactive condition. However, most cases eventually evolve into lymphoma, with 3-year survival reported at approximately 50%.[106,107] The physiologic counterpart is a peripheral T cell of unknown subset in various stages of transformation. The disorder usually presents in the sixth or seventh decade of life with fever, generalized lymphadenopathy (sometimes massive), weight loss, hepatosplenomegaly, dysproteinemia, and skin lesions in about 40% of cases, usually a pruritic morbilliform or maculopapular rash, urticarial lesions, plaques and nodules, or acral petechiae. Some cases are associated with drug use, including penicillin, griseofulvin, phenytoin, sulfonamides, aspirin, and halothane.[106] The histologic features in the lymph nodes are distinctive. The nodular skin lesions are similarly composed, with dense dermal and subcutaneous infiltrates of large immunoblastic lymphocytes admixed with plasma cells and eosinophils.[108] The histologic features of the maculopapular eruptions are usually nonspecific, with perivascular lymphocytic infiltrates with occasional atypical lymphocytes. Lymphocytic[91] and leukocytoclastic[107] vasculitis has been reported. Vascular hyperplasia may be appreciated. Identical clonal TCR gene rearrangements can be identified in maculopapular or infiltrated skin lesions and affected lymph nodes of patients with AILD.[107] EBV has been detected within affected lymph nodes and, less commonly, cutaneous lesions of some cases, but EBV is not clearly pathogenic.[107,109-111]

Pleomorphic T-cell lymphoma

Termed "pleomorphic small/medium-sized CTCL" by EORTC, PTL accounts for fewer than 3% of primary CTCL cases and is associated with an intermediate 5-year survival of 62%.[12] In one recent series, PTL comprised 3% of all primary cutaneous lymphomas.[69] Patients with pleomorphic small cell–type lymphoma have a better prognosis. The physiologic counterpart is an unspecified peripheral T-cell subset. Typically, PTL presents in adults as asymptomatic, solitary or localized but usually widespread, red-purple nodules whose size ranges from 5 mm to 15 cm without patches. Lymphadenopathy is variable and is usually reactive histologically.[112] Histologically, PTL exhibits dense and nodular, diffuse, perivascular, or periadnexal infiltrates in the papillary dermis, reticular dermis, and/or subcutis. Infiltrates of PTL contain a pleomorphic population of small and medium-sized lymphocytes with irregular, hyperchromatic nuclei (without cerebriform configuration), occasional mitotic figures, and scant cytoplasm. Large lymphocytes may be present but comprise less than 30% of the infiltrate. Epidermotropism, angiocentricity, eosinophils, neutrophils, plasma cells, and granulomatous features are variable findings.[68,112] Most cases are $CD3^+/CD4^+/CD5^+/CD7^-$. CD2 expression is variable, and CD8 is usually negative. $CD4^+/CD56^+$ lymphomas with similar histologic features but negative for other T-cell markers appear to have a poorer prognosis.[94] Clonal TCR gene rearrangements are present.

Lennert's lymphoma

Also known as lymphoepithelioid lymphoma, LL is a rare systemic $CD4^+$ T-cell lymphoma not designated in current classifications, except within the heading of unspecified peripheral T-cell lymphoma.[113] LL usually presents in adults with lymph node involvement and is classified as low-grade until transformation to large-cell lymphoma intervenes. Cutaneous lesions may be papules, plaques, or nodules (but not patches as in MF) and occur in fewer than 10% of cases.[114] Skin lesions in LL do not always represent lymphoma cutis because nonspecific inflammatory reactions and palisaded granulomatous infiltrates have also been reported.[115] Reactive epithelioid histiocytes accompany smaller $CD4^+$ MF-like T cells, although the histologic diagnosis is based primarily on the characteristic epithelioid histiocytes surrounding the neoplastic T cells. Thus distinction from granulomatous MF depends on clinical features. One series reported several cases with a cytotoxic T-cell phenotype.[116] TCR β-chain genes are clonally rearranged.[117]

CUTANEOUS B-CELL LYMPHOMAS: CHARACTERISTICS

Marginal zone lymphoma

Although universal consensus classification is absent regarding its terminology, MZL appears to be the most commonly applied. Alternative nomencla-

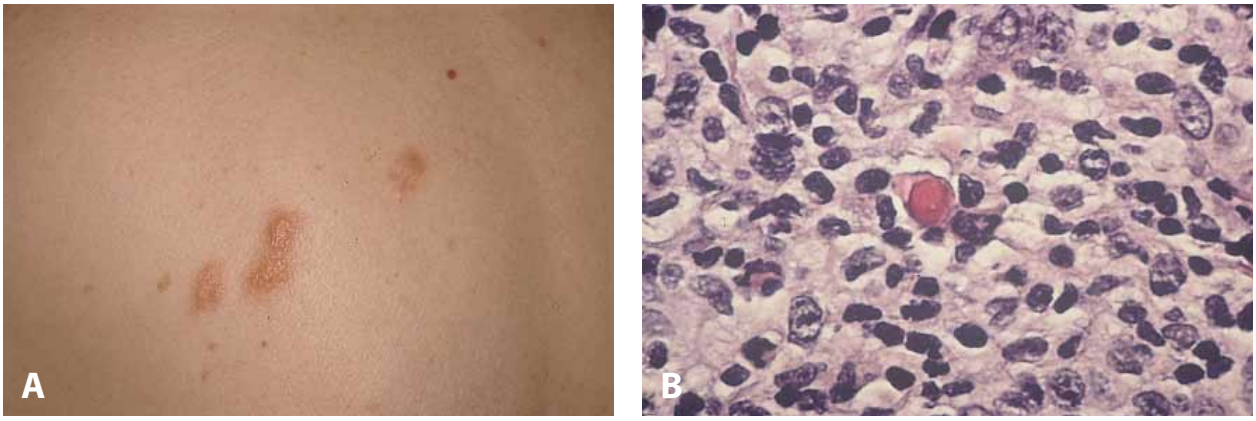

Fig 5. MZL. **A,** Plaques on the upper back of a 74-year-old woman. **B,** Intranuclear inclusion of immunoglobulin (Dutcher body) in MZL.

ture associated with MZL includes marginal zone lymphoma of MALT type, MALToma or SALToma (*s*kin-*a*ssociated *l*ymphoid *t*issue), primary cutaneous immunocytoma, and monocytoid B-cell lymphoma (reserved for primary nodal lymphoma). MZL may represent the most common form of primary CBCL and is classified by EORTC as an indolent process with 5-year survival of 100% for primary cutaneous lesions, unless transformation to large-cell lymphoma intervenes.[118] Secondary cutaneous MZL, representing spread from a nodal or extranodal primary site, is also usually indolent, although incurable, and transformation to large-cell lymphoma may occur. The postulated normal counterpart is a nodal or extranodal (MALT or SALT, depending on the primary site) marginal zone B cell with capacity for plasmacytic differentiation and tissue-specific homing. Primary cutaneous MZL presents with solitary or multiple asymptomatic dermal nodules or plaques (Fig 5, *A*), usually on an extremity.[119] MZL involving orbital and periorbital soft tissue has been associated with solid facial edema.[120] Widespread lesions suggest secondary spread to the skin. Individual cases of systemic MZL/immunocytoma have been associated with epidermolysis bullosa acquisita, Sjögren's syndrome, idiopathic thrombocytopenic purpura,[119] and anetoderma.[120a] Microscopically, there is a nodular, diffuse, or periadnexal infiltrate that is variably heterogeneous in composition, containing "centrocyte-like cells," which exhibit small but less indented nuclei and slightly more abundant pale or clear cytoplasm than centrocytes or the centrocytic cells of follicular lymphoma (FL). Some degree of plasmacytoid and plasmacytic differentiation is usually present, as are occasional larger cells with a large vesicular nucleus and a large, centrally situated nucleolus resembling immunoblasts. In fact, in some cases the marginal zone cells may not be easily identified and their quantity may vary between cutaneous lesions from the same person.[121] Reactive lymphoid follicles, eosinophils, T cells, and histiocytes often accompany the neoplastic cells. Amyloid deposits may occur.[119] In primary cutaneous MZL, light-chain restricted plasmacytoid lymphocytes and plasma cells tend to be aggregated around the peripheries of nodular infiltrates.[119] In cases containing plasmacytic differentiation, eosinophilic intranuclear (Dutcher body) or intracytoplasmic (Russell body) inclusions of immunoglobulin may be seen. Dutcher bodies may be a somewhat specific but not sensitive feature of MZL (Fig 5, *B*),[122,123] whereas Russell bodies are seen in other disorders with plasmacytic infiltrates, including Rosai-Dorfman disease (sinus histiocytosis with massive lymphadenopathy) and rhinoscleroma. Lymphoepithelial lesions, a characteristic feature of MZL in MALT, are sometimes seen in cutaneous infiltrates and resemble the epidermotropism characteristic of CTCL. MZL label with monotypic cytoplasmic immunoglobulin ($_c$Ig), CD19, and CD79α. CD20 is negative on plasma cells and some plasmacytoid cells. There is variable aberrant expression of CD11c and the T-cell marker CD43. Cytoplasmic light-chain restriction is apparent in formalin-fixed tissue by immunoperoxidase (or in situ hybridization for light-chain mRNA) in the preponderance of cases with plasmacytoid or plasmacytic differentiation. Cases that have more homogeneous populations of centrocyte-like cells label variably for surface/cell membrane immunoglobulin ($_s$Ig) and/or $_c$Ig. *Bcl*-2 expression unassociated with t(14;18) translocation has been reported.[124] Clonal rearrangement of immunoglobulin genes is present. Trisomy 3 and t(11;18) have been reported in extranodal cases.

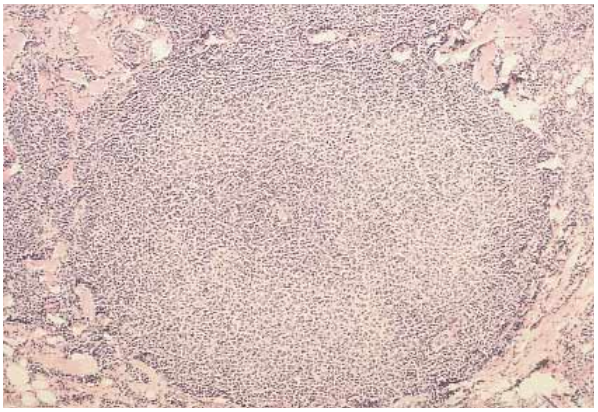

Fig 6. Neoplastic lymphoid follicles in FL.

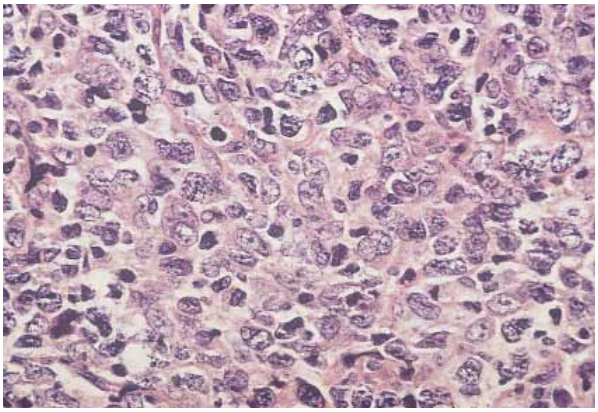

Fig 7. Cutaneous LBCL.

Follicular lymphoma

Renamed in the WHO classification, FL is an indolent CBCL that may be primary or secondary in skin. Equivalent terms include follicle center lymphoma (FCL) in the REAL classification and follicle center cell lymphoma (FCCL), although consensus is absent regarding criteria for distinguishing primary cutaneous FCCL, as defined in the EORTC classification, from primary cutaneous MZL. Thus some observers believe that cases classified as primary cutaneous FCCL might be more accurately classified as MZL. In primary cutaneous FCCL, the 5-year survival is 97%.[12] Secondary cutaneous FL represents advanced disease with a poorer prognosis. The postulated normal counterparts are centrocytes and/or centroblasts of the reactive follicle center in lymph nodes. Human herpesvirus-8 DNA sequences have been detected in some FL and MZL cases but may represent epiphenomena.[125] The skin lesions resemble those of MZL except they are usually located on the head and neck region or upper trunk rather than the extremities. The lesions may be surrounded by annular erythema and usually increase gradually in size over time. Dissemination of primary cutaneous lesions is uncommon but has been reported.[126] Microscopically, FL exhibits a nodular or diffuse pattern composed of varying proportions of small and large cells sometimes associated with reactive or neoplastic lymphoid follicles (Fig 6). Cutaneous FCCL often lacks a follicular growth pattern.[12] (The converse is also true: other types of B-cell lymphoma may exhibit a follicular pattern of growth.) Small centrocytes predominate in low-grade FL. Intermediate- and high-grade FLs have progressively higher percentages of large cells, although the risk of dissemination in high-grade primary cutaneous examples does not appear to be greater as is the case with nodal FL. Cells are reactive with pan-B cell markers and monotypic $_{s}$Ig. Expression of CD10 or *bcl*-2 is negative in FCCL as defined in the EORTC classification, in contrast to traditional criteria for nodal FL. In contradistinction to some cases of MZL, FLs are $_{c}$Ig, CD11c, and CD43 negative. Clonal rearrangement of immunoglobulin genes is present.

(Diffuse) large B-cell lymphoma

LBCLs are high-grade lymphomas histologically, but histologic grade does not appear to correlate with prognosis in primary cutaneous disease. LBCL is also a "lumper's" diagnosis, since immunoblastic lymphoma has been united with high-grade FL under this heading, at least until a clinically relevant basis for further subclassification can be established.[127] Primary cutaneous lesions of LBCL that arise on the head and neck are indistinguishable from high-grade FL and may be managed with equal success. The EORTC recognizes a distinctive subset arising on the leg associated with an "intermediate" prognosis and a 5-year survival of 58%.[12,128] Reticulohistiocytoma of the dorsum (of Crosti) describes plaques of LBCL arising on the back. Nodal LBCL is an aggressive, high-grade systemic lymphoma that may secondarily involve skin. The postulated normal counterpart is a proliferating B cell, which may be of peripheral (ie, immunoblast) or of germinal center (ie, centroblast) origin. Clinically, LBCL presents as red or purple papules, nodules, or plaques. Solitary or localized lesions are typical of primary cutaneous LBCL, whereas widespread lesions suggest primary nodal disease.[91] Histopathologically, LBCL exhibits a diffuse monomorphous dermal and/or subcutaneous proliferation of large atypical lymphocytes resembling immunoblasts or centroblasts (Fig 7). Rarely, epidermotropism has been described.[129] The cells have large vesicular nuclei with prominent nucleoli and abundant indistinct or basophilic cytoplasm. Immunophenotypically identical cells exhibit-

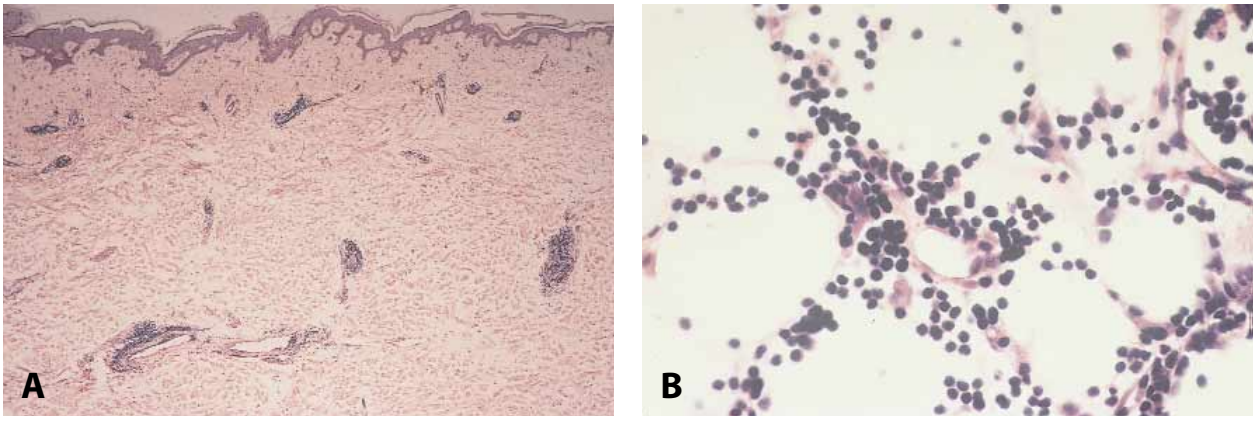

Fig 8. CLL. **A,** Sparse cutaneous perivascular infiltrates. **B,** Infiltrates of small, round, monomorphous lymphocytes in the subcutis.

ing spindled, twisted, or elongated nuclei and scant cytoplasm may predominate in some foci.[130] Other cases exhibit a majority of large cleaved centrocytic cells.[127] Typically, immunoblasts exhibit a larger, more centrally located nucleolus, and more basophilic cytoplasm compared with a centroblast, though distinguishing their neoplastic counterparts is more difficult. Plasmacytoid differentiation, anaplastic cytology, and folded/indented nuclei may be observed. Ulceration, epithelial necrosis, and numerous mitotic figures are usually present. Variable features include pseudocarcinomatous epithelial hyperplasia and infiltration of the epidermis. The cells usually express CD19, CD20, CD79α, and variably monotypic $_{s}$Ig or $_{c}$Ig. *Bcl*-2 is strongly expressed in LBCL of the leg and in about 30% of nodal LBCL[15] (although not associated with the t(14;18) translocation). Clonal rearrangement of immunoglobulin genes is present.

Chronic lymphocytic leukemia

A significant peripheral lymphocytosis is requisite for the diagnosis of chronic lymphocytic leukemia (CLL) versus small lymphocytic lymphoma (SLL), and associated skin lesions are nearly always secondary to CLL or primary nodal SLL that has disseminated to skin. The postulated normal counterpart has been regarded as a recirculating $CD5^{+}/CD23^{+}$ B cell resembling the cells comprising primary (naive) lymphoid follicles, although in some cases the cells differentiate toward memory B cells,[131] exhibiting somatic mutations of the variable regions of the immunoglobulin gene. CLL is incurable but remains indolent until transformation to large-cell lymphoma intervenes (Richter's syndrome). T-CLL is rare but is generally more aggressive than B-CLL. CLL arises in older adults and is often asymptomatic. Cutaneous manifestations include localized or generalized erythematous papules, plaques, nodules, tumors, diffuse infiltrates, or leonine facies. Bullae and vesicles may overlie plaques. Occasionally lesions will be confined to an area of previous herpes zoster or herpes simplex infection.[132] Three histologic patterns may be encountered: superficial and deep perivascular infiltrates (Fig 8), bandlike or interstitial infiltrates resembling other forms of leukemia cutis, and nodular and diffuse infiltrates. All 3 patterns spare the epidermis. CLL cells are small lymphocytes with round nuclei, dense chromatin aggregated against the nuclear membrane, small nucleoli, and scant cytoplasm. Diffuse infiltrates may contain zones of cells with paler nuclei, termed "proliferation centers" or "pseudofollicles." Plasmacytoid differentiation or Dutcher bodies may be noted. A predominant T-cell infiltrate may rarely occur in B-CLL.[133] B-CLL cells label with monotypic $_{s}$IgM, CD19, CD20, and CD79α. Labeling for CD23 and aberrant reactivity of some antibodies againt the T-cell markers CD5 and CD43 are particularly useful for this diagnosis.[132] PCR detects clonal rearrangement in immunoglobulin genes and sometimes the *bcl*-1 gene, resulting from a t(11;14) translocation. The presence of trisomy 12, significant CD38 expression, and absence of immunoglobulin V region somatic mutation may correlate with poor prognosis.[134,135] T-CLL/SLL expresses CD7 and other T-cell–associated antigens and is negative for CD25.[15]

Plasmacytoma/myeloma

Plasmacytoma may represent an isolated bone marrow or extramedullary (including skin) lymphoma but more often arises secondary to systemic disease (multiple myeloma) in about 2% of such cases.[91] Primary cutaneous and other extramedullary lesions have a lower rate of progression to multiple

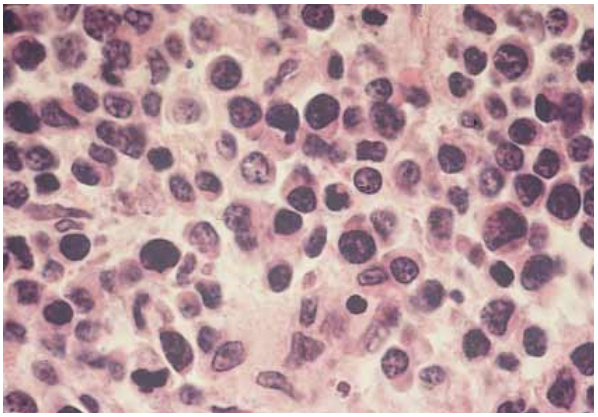

Fig 9. Cutaneous plasmacytoma.

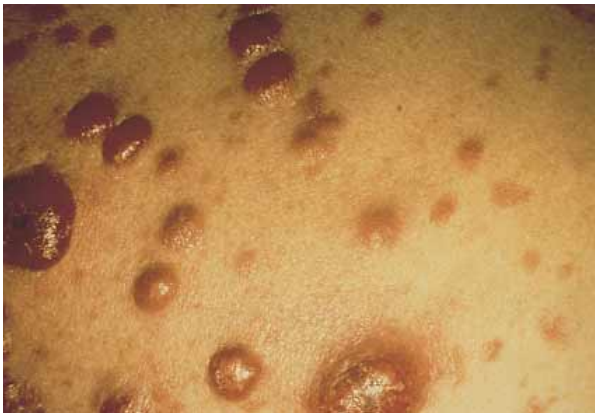

Fig 10. Lymphoblastic lymphoma.

myeloma, probably because of early detection. Thus isolated cutaneous lesions are potentially curable (5-year survival >90%),[68] whereas myeloma is generally fatal. The postulated normal counterpart is the plasma cell. Cutaneous plasmacytomas usually present as violaceous papules, nodules, or plaques. Manifestations of systemic involvement include bone pain, fractures, renal failure, amyloid deposits, monoclonal immunoglobulin or light chain in urine and peripheral blood, and plasma cell leukemia. Myeloma may also potentially arise in association with other acute or chronic skin diseases, including chronic pruritus, chronic urticaria, Sweet's syndrome, pyoderma gangrenosum, leukocytoclastic vasculitis, erythema elevatum diutinum, subcorneal pustular dermatosis (Sneddon-Wilkinson disease), POEMS (*p*olyneuropathy, *o*rganomegaly, *e*ndocrinopathy, *M* protein, *s*kin lesions) syndrome, scleromyxedema, necrobiotic xanthogranuloma, and plane xanthomas. Myeloma may arise after solid organ transplantation.[136] Unlike other types of lymphoma in which focal plasmacytic differentiation may be observed, plasmacytomas have dense nodular or interstitial monomorphous infiltrates of plasma cells and no recognizable areas with other types of lymphocytes (Fig 9). Mitotic figures are common. The neoplastic cells may resemble the classic Marschalko-type plasma cell or immunoblastic or anaplastic large cells (plasmablasts). The proportion of large cells and the degree of nuclear atypia may correlate directly with a poorer prognosis. Eosinophilic intranuclear (Dutcher body) or intracytoplasmic (Russell body) inclusions of immunoglobulin, as seen in MZL, are uncommon. Plasmacytomas express monotypic $_{c}$IgG, $_{c}$IgA, κ or λ light chain, or rarely $_{c}$IgD or $_{c}$IgE. $_{s}$Ig is negative. CD79α is variably expressed and CD19 and CD20 are negative. EMA, CD43, and CD30 are also variably expressed. Clonal rearrangement or deletion of Ig heavy (IgH) and light chain (IgL) genes is demonstrable.

Mantle cell lymphoma

Cutaneous lesions of mantle cell lymphoma (MCL) are rare and represent secondary cutaneous lesions until proved otherwise. Primary cutaneous lesions apparently do occur, may be underrecognized, and may not be as indolent as MZL. Nodal MCL is classified as "moderately aggressive" and incurable in the REAL classification with a median survival of 3 to 5 years.[15] The postulated normal counterpart is the $CD5^{+}$/$CD23^{-}$ follicle mantle zone cell of reactive lymph node follicles. Clinical descriptions are rare, but dome-shaped red-purple plaques or nodules with smooth or "vegetating" surfaces have been described on the conjunctiva, head, trunk, and extremities.[137,138] MCL may display patchy rather than diffuse and "top-heavy" infiltrates of small to medium-sized lymphocytes that resemble the cells of CLL/SLL or MZL with round or irregular nuclei, inconspicuous nucleoli, dense or slightly dispersed nuclear chromatin, and scant pale cytoplasm. The "mantle-zone" growth pattern is expansion of the mantle zone area surrounding and seemingly compressing the center of a reactive lymphoid follicle. Because this growth pattern is not alway present, the designation "mantle cell lymphoma" is preferable to "mantle zone lymphoma."[15,139] Large lymphocytes are rare, except in the blastoid variant. MCL cells are generally $CD5^{+}$/$CD23^{-}$/$_{s}IgM^{+}$/$_{s}IgD^{+}$/$CD43^{+}$. A t(11;14) translocation is present in most cases of nodal MCL resulting in apposition of the IgH and *bcl*-1 loci, resulting in overexpression of cyclin D1.

B-lymphoblastic lymphoma

Cutaneous lesions of B-lymphoblastic lymphoma (B-LBL) are rare and should be considered sec-

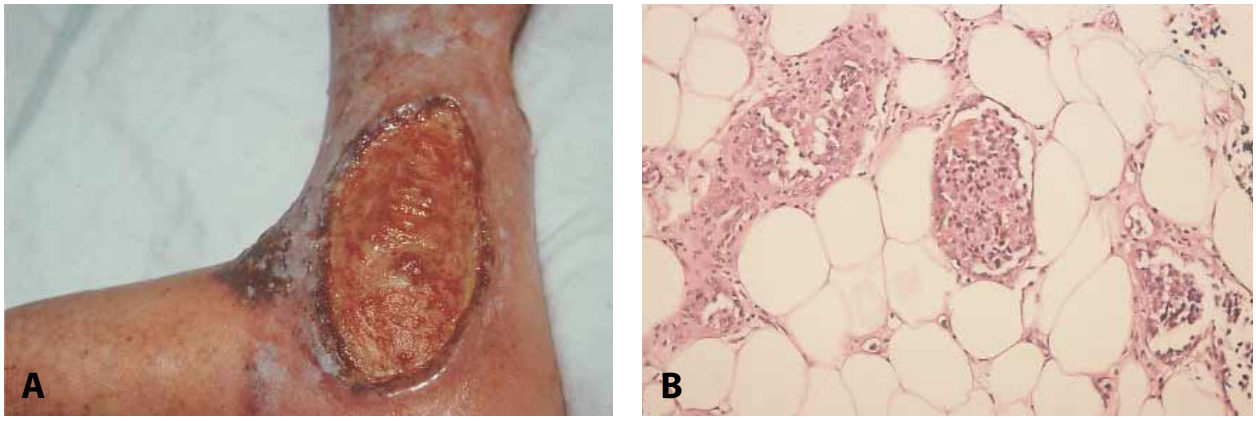

Fig 11. Intravascular lymphoma. **A,** Chronic leg ulcer. **B,** This patient's biopsy specimen revealed large atypical B cells within blood vessels. (**A,** Courtesy of George J. Murakawa, MD, PhD, Detroit, Mich.)

ondary cutaneous lesions until proved otherwise. Significant peripheral lymphoblastosis (>25%) indicates a diagnosis of acute lymphoblastic leukemia (ALL) in most, but not all, cases. B-LBL accounts for only 10% of all LBLs (the remainder are T-LBL) but represents the majority of cutaneous lesions. Currently there does not appear to be a significant clinical or pathologic difference between LBL of T- or B-cell lineage, although B-ALL has a better prognosis than T-ALL, and accurate discrimination between lymphoma and leukemia cannot always be achieved. LBL is a clinically aggressive, histologically high-grade lymphoma with a median survival of 12 months. Prognosis is more favorable in those with isolated cutaneous involvement. LBL usually presents in children and adults as solitary or multiple erythematous or purpuric papules and nodules on the head and neck (Fig 10).[91,140,141] Histologically, LBL presents as a nodular or diffuse proliferation of small to medium-sized cells with round or convoluted nuclei, thin but well-defined nuclear membranes, fine chromatin, inconspicuous nucleoli, and scant basophilic cytoplasm. Tingible body-type macrophages are sometimes interspersed, resulting in a "starry sky" pattern. T-LBL and B-LBL are indistinguishable without immunophenotyping. LBL cells express terminal deoxynucleotidyl transferase. B-LBL will also label with CD10, CD19, CD20, CD79α, and often $_{c}$Ig. T-LBL expresses $_{c}$CD3, CD7, CD45RO and variably CD4, CD5, and CD8. CD4 and CD8 are often both positive ("double positive") or both negative. The NK marker, CD56, is rarely expressed.[142] Gene rearrangement studies are clonal, but TCR rearrangements are occasionally seen in B-LBL, and immunoglobulin rearrangements may be seen in T-LBL.

Intravascular lymphoma

Previously known as "malignant angioendotheliomatosis," intravascular lymphoma was considered a vascular proliferation. This form of CBCL generally has a poor prognosis, but primary cutaneous cases may demonstrate a more favorable clinical course. The estimated 5-year survival published by EORTC is 50%.[12] The skin is commonly involved, usually with smooth hemorrhagic, indurated patches and plaques on the trunk or extremities, particularly the lower legs where it resembles panniculitis that may eventuate in ulceration (Fig 11). The central nervous system is also commonly involved with fever and dementia; there also are visual, speech, or sensory abnormalities. Mass lesions and lymphadenopathy are often absent.[91] One case was diagnosed by sampling a cutaneous cherry angioma.[143] Intravascular lymphoma cells are cytologically atypical often with large vesicular nuclei, multiple nucleoli, irregular nuclear contours, and visible cytoplasm, like the cells that make up LBCL. In fact, one case of LBCL of the leg relapsed as intravascular lymphoma.[17] The cells are situated within the lumens of venules, capillaries, and arterioles of the dermis and subcutis, associated with fibrin; however, slight interstitial extension of cells occurs in only 20% of cases.[12] Cells label with CD19, CD20, CD22, CD79α, and $_{s}$Ig. T-cell immunophenotypes occur less commonly. Immunoglobulin genes are clonally rearranged.

Hodgkin's disease

HD is unique among nodal lymphomas for its (1) lack of lineage-specific markers, (2) characteristic cell (Reed-Sternberg) and other unique histologic features, (3) and the tendency to spread locally. HD is rare in skin, usually presenting in the setting of advanced nodal or visceral disease as an indicator of

poor prognosis. Single-cell gene rearrangement studies suggest that HD typically represents a form of BCL,[144,145] but the postulated normal counterpart(s) is (are) unknown, possibly a follicle center cell with defective immunoglobulin production. TCR gene rearrangements occur less commonly.[146] Cutaneous HD usually presents as papules, plaques, or nodules within an upper or lower extremity distal to involved lymph nodes.[147-149] Generalized pruritus or prurigo nodularis may be associated.[150-152] The 4 general histologic types are lymphocyte-predominant, nodular sclerosing, mixed cellularity, and lymphocyte-depleted. Cutaneous HD is usually a nodular or diffuse infiltrate sparing the epidermis and exhibiting the histologic features of nodal disease. Reed-Sternberg cells are large binucleate cells with vesicular nuclei, prominent eosinophilic nucleoli ("owl eyes appearance"), and clumped chromatin (Fig 12). Similar mononucleate cells are termed Hodgkin's cells. These cells are outnumbered by a reactive inflammatory infiltrate of small lymphocytes, eosinophils, neutrophils, and plasma cells, depending on the variant. Lymphocyte-predominant HD rarely involves the skin. Nodular sclerosing HD contains lacunar ("popcorn") cells, which contain multilobated nuclei with surrounding retraction artifact. Lymphocyte-depleted HD demonstrates necrosis and more monomorphous infiltrates of Reed-Sternberg and Hodgkin's cells.[15,91] The hallmark is expression of CD30 and CD15 by Reed-Sternberg cells. The differential diagnosis includes $CD30^+$ large T-cell lymphoma (containing Reed-Sternberg–like cells) and LyP. However, cutaneous involvement by HD is generally indicative of systemic disease, and LyP and primary cutaneous large T-cell lymphomas are usually $CD15^-$. As previously mentioned, cases diagnosed as primary cutaneous HD may be indistinguishable from LyP.[82]

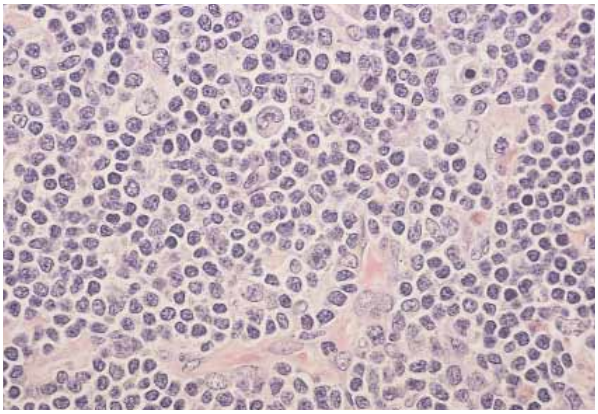

Fig 12. HD. Large lymphocytes with prominent nucleoli scattered among smaller reactive lymphocytes.

THERAPY: CUTANEOUS T-CELL LYMPHOMA

For practical purposes, therapy for CTCL is currently dependent on the clinical stage rather than on the specific subtype, although the vast majority of data relates to treatment of patients diagnosed with either MF or SS. The tumor, node, metastasis, blood (TNMB) system is used to determine overall clinical stages, I through IV (see Tables I and IV). Although some patients with localized primary cutaneous lymphoma may have been cured, therapy for CTCL is oriented toward achieving and maintaining clinical remission and, in advanced cases, palliation. Controlled trials associating a survival benefit with any particular therapy do not yet exist. Additional perspectives regarding management and therapy have been published.[21,153-155]

Established successful practice patterns have been developed at the major referral institutions for CTCL, although their individual preferences and methods vary. In the absence of controlled trials, assumptions exist that (1) available therapies reduce morbidity and possibly mortality in CTCL, (2) clinically visible disease should be actively treated, and (3) patients in remission should be followed up indefinitely. Whether maintenance therapy for patients in complete remission is advantageous is equivocal, although such maintenance therapy is routine at some centers.

There is general agreement regarding the therapies available (Table VI), but with few exceptions impressions about relative efficacy are based on nonrandomized, uncontrolled outcomes. Many of the most commonly utilized therapies are not specifically indicated for CTCL by the Food and Drug Administration (FDA). In the single most influential randomized trial to date, investigators found that aggressive treatment (combination chemotherapy and total skin electron beam therapy [TSEB]) does not offer a survival benefit in early-stage CTCL when compared with topical therapy.[156]

Topical therapy

Topical therapy is appropriate for limited (T1) or generalized (T2) patches and plaques of MF. Topical chemotherapy with either nitrogen mustard or carmustine (BCNU) is the most popular specific first-line therapy for early MF. These agents are also used as adjuvant therapy after the achievement of complete remission with the use of TSEB.[157]

Nitrogen mustard (mechlorethamine hydrochloride) solution or ointment may be the most widely used topical agent in CTCL, with an 88% total response rate (51% complete response) in stage T1.[158] Use of nitrogen mustard has been limited by a

Table VI. Therapy for CTCL

Modality	Use (disease stage)	Topical	Photo-therapy	Photochemo-therapy	Radiation	Oral	IL	SQ	IM	IV
Corticosteroids	T1-2	X				X				X
Nitrogen mustard	T1-2	X								
Carmustine (BCNU)	T1-2	X								
UVB	T1-2		X							
PUVA	T1-2			X		X				
Photopheresis	T2-4			X						X
Methotrexate	T2-4					X		X	X	X
Bexarotene, gel	T1-2	X								
Bexarotene, oral	T1-4					X				
Acitretin	T1-4					X				
IFN-α	T1-4						X	X	X	
IFN-γ	T1-4						X	?	X	X
Electron beam therapy: localized	T1-3				X					
Electron beam therapy: total skin	T2-4				X					
Orthovoltage radiation: localized	T1-3				X					
Denileukin diftitox	T2-4									X
Other single agent or combination chemotherapy	T2-4									X

bid, Twice daily; *IL*, intralesional; *IM,* intramuscular; *IV,* intravenous; *qd,* once daily; *SQ,* subcutaneous.
[a]Retail price, Yale Medical Center Pharmacy, New Haven, Conn (July 2001).
[b]Department of Dermatology, University of Connecticut (July 2001).
[c]Does not include cost of psoralen.
[d]Photopheresis unit, Department of Dermatology, Yale University, New Haven, Conn (July 2001).
[e]Average wholesale price, University of Connecticut Health Center, Farmington (August 2000).
[f]Assume 10% body surface area involvement (approximately 3 g/application).
[g]Assume 3 treatments per week.
[h]Assume 2 treatments per month.
[i]Assume dose of 20 mg by mouth per week.
[j]Assume dose of 300 mg/m^2 with a body surface area of 1.0 m^2.
[k]Assume dose of 25 mg/d.
[l]Assume dose of 3×10^6 U, 3 times per week.
[m]Assume dose of 18 μg/kg per day for 5 days per month, body weight of 70 kg.

frequency of allergic contact dermatitis ranging from 30% to 80%,[159] although the ointment preparation appears to be associated with a lower incidence of this complication.[160] Rare complications of nitrogen mustard therapy include localized bullous reactions,[161] urticarial, anaphylactoid,[162] and Stevens-Johnson–type reactions.[163] BCNU ointment or solution appears to have comparable efficacy when compared with nitrogen mustard with a 98% total response rate (86% complete response) in stage T1.[164] In comparison with nitrogen mustard, there is a lower frequency of contact dermatitis,[165] but BCNU often leaves persistent telangiectasia at treated sites.[166] In addition, mild leukopenia has been associated in 3% to 5% of patients treated with BCNU solution or ointment.[153] In either case, a 2- to 6-month trial of daily application of solution (either lesional or total body surface) or a 6- to 12-month trial is suggested.[153] Both should be kept refrigerated[166,167] and are available from several pharmacists, including Crown Drugs (Philadelphia, Pa) or the Yale Medical Center Pharmacy (New Haven, Conn). As an additional reference, Zackheim's recent review[168] of topical chemotherapy is suggested.

Corticosteroids have been used for early MF at least since the 1960s.[169-171] Recently their efficacy was reported in a large series, with total response rates of 94% (complete response, 63%) in T1 disease, which is comparable to the results seen with topical chemotherapy.[172] The complete response rate decreased to 25% in T2 disease. One patient with T1 disease who was refractory to multiple alternative modalities achieved complete remission with corticosteroids. Most patients were treated with clobetasol propionate emollient cream. Data comparing corticosteroids and long-term follow-up are not yet available. Other corticosteroids have reportedly been used for MF, including fluocinolone acetonide under occlusion,[169] triamcinolone,

Cost (US $)/Quantity	Monthly cost example (US $)
48/45 g (clobetasol propionate ointment)[a]	192[f] (bid)
42/60 g 10 mg/dL ointment[a]	63[f] qd
42/60 g ointment[a]	63[f] qd
480/12 sessions[b]	480[g]
600/12 sessions[b,c]	600[g]
3900/1 session[d]	7800[h]
98/#30 (2.5 mg)[a]	104[i]
1100/60 g gel[a]	3300[f] bid
550/#30 (75 mg)[a]	2200[j]
413/#30 (25 mg)[a]	413[k]
$35/3 \times 10^6$ U (RoferonA)[e]	420[l]
$992/300 µg[e]	20,832[m]

fluocinonide, diflorasone diacetate, halobetasol propionate, and betamethasone valerate.[172] Advantages of corticosteroids compared with topical chemotherapy include ease of application, superior product stability, reduced carcinogenicity, increased familiarity with use and side effects, and possibly reduced cost and increased compliance.

Bexarotene 1% retinoid gel (Targretin) was recently approved by the FDA, with an overall response rate of 44% to 63% (complete response, 8%-21%) in patients with refractory stage Ia-IIa CTCL.[173,174] The predominant side effect is mild to moderate local irritation or rash.

With all topical therapy, the complete response rate drops to below 50% in T2 disease.[172]

Phototherapy

Each of the methods outlined in this section generally has a superior complete response rate when compared with topical modalities in stage T2 MF, although broad-band ultraviolet B (UVB) phototherapy is largely ineffective for infiltrated plaques.[175]

Traditional broad-band UVB phototherapy (280-320 nm) has been associated with an 83% total and complete response rate in T1 disease.[175] More recently, narrow-band UVB (TL-01, 311 nm)[176,177] and UVA1 (340-400 nm) phototherapy have been used for early MF[178] as well as more advanced stages[179] with good short-term responses in a limited number of patients.

Oral photochemotherapy (PUVA) is a well-established modality for early MF, with the largest series reporting total response rates of 95% (complete response in 79% of T1 cases, 59% of T2 cases). Duration of remission averaged 3.6 years with maintenance PUVA at least once per month.[180] One possible advantage of PUVA is that complete remission appears to occur faster compared with topical therapy. There is usually a negligible response, or a short-lived or partial response, in T3 and T4 disease.

Extracorporeal photochemotherapy (photopheresis) is FDA-approved for refractory CTCL.[181] It involves extracorporeal photoactivation of 8-methoxypsoralen-enriched leukocytes from the patient's peripheral blood. The irradiated cells are then returned to the patient. A typical regimen is 2 consecutive days per month. Overall, total and complete response rates have been reported at 50% and 25%, respectively, with clinical responses within the first 6 to 8 months associated with greater long-term survival.[182] Some investigators consider absence of a peripheral clone to be a contraindication to use of this modality.[183] Photopheresis may be most effective when used before immunosuppressive chemotherapy, since a competent immune system may be required for optimal response.[185] Reports are inconsistent regarding the survival benefit of photopheresis, particularly in SS, compared with other modalities[183,184]; hence the need for a randomized, multicenter trial has been emphasized.[186] However, investigators continue to explore methods for optimizing the photopheresis protocol.[185]

Radiation therapy

Radiotherapy is useful for definitive treatment of a variety of primary CTCL types, including MF tumors, pagetoid reticulosis, large T-cell lymphoma, or PTL. For cutaneous lesions associated with systemic disease, radiotherapy may play a palliative role. Megavoltage photon irradiation may be used in combination with chemotherapy or other regimens for patients with nodal involvement.

TSEB therapy may be the single most reliable method for inducing complete clinical remission in

Table VII. Examples of combination and sequential therapy in CTCL

Stage	Therapies
Ib-IIb	TSEB f/b topical nitrogen mustard[157,191] PUVA + retinoid[201]
Ib-IVb	PUVA + interferon[217,220]
Ia-IVb	Interferon + retinoid[35,243-245]
Ib-IVb	Interferon + photopheresis[183,219]
Ib-IVb	Interferon + photopheresis + retinoid[183]
Ib-IVb	Interferon + photopheresis + topical nitrogen mustard[183]
IVb	Interferon + photopheresis + IL-2[220]
IIb-IVb	Multiple-agent chemotherapy + etretinate[246]
I-II	Interferon + isotretinoin f/b TSEB[247]
IIb-IVa	TSEB f/b multiple-agent chemotherapy + maintenance therapy[248,249]
III-IV	Multiple-agent chemotherapy f/b interferon + topical nitrogen mustard[247]
III-IVb	TSEB + photopheresis[189]

f/b, Followed by.

generalized patches, plaques, and tumors of MF, with complete response rates of up to 98% for limited plaques and 36% for tumors in the largest reported series.[187] The majority of patients have a relapse within 5 years.[187,188] TSEB has been recommended as first-line therapy for MF-associated follicular mucinosis.[12] Some consider TSEB too toxic for first-line therapy in erythrodermic MF and SS,[187] but TSEB may be effective in erythroderma, particularly when combined with photopheresis.[189] Availability of TSEB is generally limited to regional referral centers, although electron beam therapy for localized lesions is more widely available. Many patients will tolerate a second course of TSEB, but remissions tend to be the most sustained after the first course.[189] A typical regimen consists of a cumulative exposure of 36 Gy (1.5-2.0 Gy/d) divided over a 10-week course. Common side effects include alopecia (reversible with exposure <25 Gy), erythema, desquamation, onychomadesis, xerosis, and anhidrosis (lasting 6-12 months). Some patients will develop persistent telangiectasia. After attaining complete remission with TSEB, some physicians initiate adjuvant therapy, most commonly topical nitrogen mustard or oral PUVA for at least 6 months. In this setting, adjuvant therapy with topical nitrogen mustard increases the time to relapse but has not been shown to increase survival.[190]

Single-agent systemic therapy

Treatment categories include immunomodulators, retinoids, and chemotherapy.

Interferon alfa (IFN-α) (α2a or α2b) has been used alone and in combination with numerous other modalities. Recombinant (Roferon-A) IFN-α2a is the most frequently reported single systemic therapeutic agent and is effective as intralesional, subcutaneous, or intramuscular therapy. In a randomized, blinded, placebo-controlled trial, intralesional IFN-α2b (Intron A) proved to be superior to betamethasone dipropionate ointment.[191] More than 26 publications detailing experience with interferons in more than 300 patients have been reported with an average complete remission rate of about 25% and overall response rate of up to 80%. The single best predictor of response is clinical stage at the start of therapy, with the best results for T1 or T2 disease.[192] In one study, length of remission averaged 7.5 months, with the majority of patients experiencing relapse.[193] Subcutaneous IFN-α2a, 3×10^6 U, 3 times a week or daily for a 6- to 9-month trial, is suggested. Injection near more advanced lesions is advised. Consideration should be given to combination therapy with PUVA or photopheresis (see "Combination chemotherapy"). Although most experience has been reported with subcutaneous IFN-α2a, the efficacy of IFN-α2a, recombinant and natural (Wellferon, Cilferon) IFN-α2b, and IFN-γ may be comparable and has not been subjected to a comparative trial. IFN-γ may benefit patients who are no longer responsive to IFN-α.[193] IFN-γ has also been employed in the treatment of granulomatous slack skin.[194] There is some evidence that alternating use of natural and recombinant IFN-α2b may improve or prolong efficacy because of the development of anti-IFN-α antibodies.[195] Common adverse effects of interferons include flu-like symptoms, depression, depressed blood cell counts, and elevated transaminase levels. As in the treatment of other disorders, bullous reactions have been reported.[196]

Oral bexarotene (Targretin) is a retinoid that was recently approved by the FDA for all stages of refractory CTCL. In stage IA-IIA (early) disease, the overall response rate was 48% with a complete response rate of 12% using varying doses.[197] In stage IIB-IVB disease, the overall response rate was 49% with a complete response rate of 7%.[198] A 3- to 5-month trial of bexarotene, 300 mg/m^2, is suggested. Common side effects include hypothyroidism and hyperlipidemia. Isotretinoin (Accutane) or acitretin (Soriatane) may be useful either as monotherapy[199] or in combination with calcitriol (for PTL)[201] or PUVA.[202]

Intravenous denileukin diftitox (Ontak) is a fusion toxin, DAB_{389}IL-2, that is approved by the FDA for refractory CTCL in patients whose neoplastic cells express CD25 (IL-2 receptor). Fresh-frozen tissue or peripheral blood analysis is recommended to determine CD25 status. In 35 patients with refractory

CTCL stages IA-IVB, the overall response rate was 37%, with a complete response rate of 14%.[202] A treatment cycle consists of daily infusions, 18 μg/kg per day for 5 days, and may be repeated every 3 weeks. Most patients respond within 2 to 6 cycles, although responses in patients with stage IV CTCL have not been documented. Common side effects include flu-like symptoms, nausea, vomiting, and hypotension that may be associated with a vascular leak syndrome characterized by peripheral edema and hypoalbuminemia.

Methotrexate is available by oral, subcutaneous, intramuscular, and intravenous routes and is approved by the FDA for treatment of advanced MF. More data exist for methotrexate than for any other single chemotherapeutic agent.[203] Advantages of methotrexate include low cost, familiarity with use, and side effects that are relatively well tolerated by patients, assuming at least comparable efficacy with other chemotherapeutic agents in T2-T4 disease, including SS.[204] A 2- to 4-month trial of up to 50 mg/wk is suggested. Subcutaneous injection has been recommended for doses above 25 mg because they are less painful and equivalently bioavailable when compared with intramuscular injection.[153] Low-dose methotrexate (15-20 mg/wk) may be useful in the management of LyP.[205] Higher doses (eg, 20-30 mg/wk) may be required to control primary cutaneous $CD30^+$ large T-cell lymphoma.[71,205]

Cyclophosphamide (Cytoxan), vinblastine (Velban), and systemic mechlorethamine are also approved by the FDA for advanced MF. These agents, as well as fludarabine, chlorambucil, cyclophosphamide, 2´-deoxycoformycin (pentostatin, Nipent), 2-chlorodeoxyadenosine,[206,207] gemcitabine,[208] bleomycin, etoposide, and doxorubicin,[209] have been used as monotherapy. One review[203] reported complete and overall response rates for single-agent chemotherapy at 33% and 62%, respectively, mainly in patients with refractory or stage IV disease. The combination of daily or pulsed chlorambucil with prednisone or fluocortolone for erythrodermic MF and SS has been reported.[210,211] Overall, the responses with single agents are inferior to those achieved by combinations.

Combination chemotherapy

Multiple-agent chemotherapy is reserved for refractory or advanced CTCL or systemic T- or NK-cell lymphoma. Aggressive treatment of early MF does not appear to confer a significant survival benefit.[156] Regimens include CHOP (cyclophosphamide, vincristine, doxorubicin, prednisone), CAVE (cyclophosphamide, doxorubicin, vincristine, etoposide),[156,203] or EPOCH (etoposide, vincristine, doxorubicin, cyclophosphamide, prednisone).[212] However, no single agent, combination, or sequential regimen has clearly demonstrated a survival advantage.[212] Most patients have a relapse within months.

SPTL is notoriously refractory to combination chemotherapy, radiation therapy, and various combination regimens.[100] In one case, multiple combination chemotherapeutic regimens combined with radiation therapy and below-knee amputation in a patient whose disease was localized to that extremity resulted in at least short-term remission.[213] In another case, complete remission was reported with fludarabine, mitoxantrone, and dexamethasone.[214] NK and NK-like angiocentric lymphoma,[101,215] ATL, AILD, and LL[114] are also usually treated with multiple-agent chemotherapy, although whether therapy has a significant impact on the clinical progression of these diseases is uncertain.

Generalized skin involvement in cases of apparent primary cutaneous $CD30^+$ large T-cell lymphoma should be considered for treatment with multiple chemotherapy.[66,81,216]

Combined modality therapy

Increasingly, combined modality therapy, particularly with photopheresis, interferons, and retinoids, has been explored in an attempt to improve the frequency and durability of favorable therapeutic outcomes. To date, all reports of combined modality therapy are based on retrospective case series except for one randomized trial that demonstrated that the combination of IFN-α2a with PUVA more frequently achieved complete remission when compared with interferon plus acitretin in stage I and II CTCL.[217] An overall response rate of 93% was reported using both PUVA and IFN-α2a in 15 patients with T1-T4 disease, the majority achieving complete remission.[218] However, these rates may be comparable to those achieved with PUVA alone, particularly in T1-T2 disease.[180,218] Similarly, the combination of retinoids with PUVA may achieve faster remission with lower doses of UVA, but the remission rate is not significantly improved.[201] The addition of IFN-α to ongoing photopheresis monotherapy appears to enhance the clinical response in some cases.[183,219] A case report of triple combination therapy with photopheresis, IFN-α, and IL-2 was recently reported.[220] In one case, combination therapy for stage T3 MF with pentostatin and IFN-α was complicated by hemolytic-uremic syndrome.[221]

Other combinations and sequences that have been reported are summarized in Table VII. No combined modality regimen has been shown to confer a significant survival advantage.

Other therapy

Investigational modalities that may prove useful for the treatment of CTCL include herbal therapy with Hochu-ekki-to,[222] subcutaneous or intralesional IL-12,[223] IL-2,[224] radiolabeled monoclonal antibodies targeting CD25 or CD4,[225] antitumor vaccines,[226] and peripheral stem cell or autologous bone marrow transplantation for advanced disease.[227] When feasible, surgical excision has been advocated for treatment of pagetoid reticulosis.[12]

THERAPY: CUTANEOUS B-CELL LYMPHOMA

Experience with treatment of primary CBCL is more limited, but most cases of MZL, LBCL, and the rare plasmacytoma are managed successfully with local orthovoltage radiation therapy or complete surgical removal. Controlled clinical trials have not yet been reported.

Treatment of BCL associated with extracutaneous or widespread cutaneous involvement usually requires multiple-agent chemotherapy and should be coordinated with an oncologist.

Intralesional cisplatin-epinephrine gel was reported as therapy for primary cutaneous FL.[228] Rituximab is an anti-CD20 monoclonal antibody that achieved partial remission as monotherapy and short-lived complete remission when combined with chemotherapy in a case of LBCL of the leg.[229]

PROGNOSIS

Long-term observation of patients with CTCL at Stanford University and the University of California, San Francisco, indicates that life expectancy in patients with patch-stage or limited (<10%) plaque-stage disease is essentially equal to that of age-matched control subjects.[18,19] The experience of the Dutch Cutaneous Lymphoma Group is comparable.[20] Patients in these series were treated for active disease, so whether treatment of early disease affects survival has not been established. Survival in patients with MF is improving, which in part may be related to earlier detection[18] and possibly successful therapy and increased inclusion of benign disorders as early MF.[230,231] Patients with CTCL may be at increased risk for the development of secondary malignancies,[64,232] particularly lung cancer.[233]

Other factors associated with prolonged survival include the ability to induce initial complete clinical remission and diagnosis at an early (T1) clinical stage, without lymph node, peripheral blood, or visceral involvement.[234-238] Patients with T3 and T4 disease who are older than 60 years at diagnosis or with elevated serum lactate dehydrogenase levels have been shown to have diminished median survival of approximately 3 years.[21] Whether presence of a circulating T-cell clone represents an independent prognostic factor is currently under study.[239] The major infectious causes of death in patients with MF and SS are pneumonia and bacterial sepsis.[240]

As is the case with CTCL, prognosis in CBCL hinges critically on the presence of extracutaneous lymphoma. Low-grade primary CBCLs such as MZL and FL may be essentially curable with local radiation therapy or complete excision. In fact, even plasmacytoma/myeloma and LBL, which are frequently fatal, appear to have an excellent prognosis in the rare case limited to the skin. Factors potentially associated with a poor prognosis in primary cutaneous lymphomas other than MF or SS include presence of B symptoms (ie, fever, chills, night sweats), generalized distribution of skin lesions, and elevated serum lactate dehydrogenase levels, all of which correlate with "intermediate" or "aggressive" behavior in the EORTC classification.[12]

Tumor burden index has been proposed to measure overall disease severity.[241]

CONCLUSIONS

Accurate evaluation of patients with suspected or established cutaneous lymphoma requires the correlation and integration of (1) the clinical history and physical examination; (2) histologic, immunohistochemical, and molecular diagnostic studies; (3) evaluation for systemic disease, as indicated; and (4) longitudinal observation. Diagnoses should be based on a knowledge of specific lymphoma types as described in modern classification systems, such as those proposed by the EORTC or WHO.

Proper management of patients with cutaneous lymphoma requires collaboration among dermatologists, dermatopathologists, hematopathologists, as well as medical, surgical, and radiation oncologists. Until more randomized, controlled trials produce positive results, the standard of care will continue to exist within a broad range of therapeutic options dictated by local practice patterns.

Currently, the most common presentation of CTCL is early-stage (T1, T2) MF, and only a minority of patients die of their disease.[18-20] Advanced MF and many non-MF forms of CTCL have a poorer prognosis, although primary cutaneous $CD30^+$ large T-cell lymphoma and LyP have an excellent prognosis. Patients with CBCL represent a heterogeneous group whose prognosis is generally excellent when disease is limited to the skin, but poor when associated with systemic lymphoma.

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Answers to CME examination

Identification No. 802-103

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Questions 1-30, Fung MA, Murphy MJ, Hoss DM, Grant-Kels JM. J Am Acad Dermatol 2002;46:325-57.

1. b
2. c
3. b
4. b
5. d
6. e
7. a
8. a
9. a
10. e
11. a
12. a
13. a
14. a
15. a
16. a
17. c
18. d
19. b
20. b
21. b
22. a
23. c
24. d
25. a
26. e
27. b
28. e
29. b
30. a

Appendix. Glossary

adult T-cell leukemia/lymphoma. A high-grade lymphoma induced by HTLV-I

CD #. Cluster designation; the most common prefix used to catalog the ever-growing number of lymphoid and other cell markers. Its use is not specific to lineage or to function. T-cell markers include CD2-CD8 and CD45RA, CD45RO, and CD43. B-cell markers include CD19-CD23 and CD79α.

centroblast. A small or large lymphocyte within a reactive lymph node follicle. Centroblasts have noncleaved vesicular nuclei with one or more prominent nucleoli and basophilic cytoplasm.

centrocyte. A small or large lymphocyte within a reactive lymph node follicle. Centrocytes have irregular (cleaved) nuclear contours and scant cytoplasm.

cutaneous lymphocyte antigen (CLA). Recognized by the antibody HECA-452, CLA (CD15s) is a marker for the skin-homing subset of circulating T cells (Robert C, Kupper TS. Inflammatory skin diseases, T cells, and immune surveillance. N Engl J Med 1999;341:1817-28).

cutaneous B-cell lymphoma. Primary or secondary in skin

cutaneous T-cell lymphoma. Primary or secondary in skin

chronic lymphocytic leukemia/small lymphocytic lymphoma. SLL is a nodal lymphoma exhibiting, in most cases, the characteristic morphologic, immunophenotypic, and cytogenetic features of its putative physiologic counterpart, a recirculating $CD5^+/CD23^+$ B cell.

Dutcher body. Intranuclear deposit of immunoglobulin; may be a feature of MZL or CLL/SLL

epidermotropism. Lymphocytes in the epidermis; most characteristic of patch- and plaque-stage MF, but also seen in ATL and reactive infiltrates. There is disproportionately little, if any, associated spongiosis compared with a spongiotic dermatitis. "Basalar epidermotropism" refers to the tendency for lymphocytes to accumulate near the basal layer of the epidermis in MF (Weedon D. Skin pathology. New York: Churchill Livingstone; 1998. p. 932; *also* Maize JC, Burgdorf WH, Hurt MA, LeBoit PE, Metcalf JS, Smith T, et al. Cutaneous pathology. New York: Churchill Livingstone; 1998).

epithelial membrane antigen (EMA). A glycoprotein found in normal epithelium, but also in a variety of carcinomas, sarcomas, plasma cells, some plasmacytoid lymphomas, and some $CD30^+$ large T-cell lymphomas

exocytosis (lymphocytic). Lymphocytes in the epidermis; usually seen in nonneoplastic infiltrates but also seen in CTCL. Lymphocytes are typically dispersed at all levels within the epidermis and there is associated spongiosis (Weedon D. Skin pathology. New York: Churchill Livingstone; 1998. p. 932). (However, some use this term to refer to the presence of lymphocytes in the epidermis irrespective of the presence of spongiosis, in which case the terms "exocytosis" and "epidermotropism" would be synonymous [Smoller BR, Bishop K, Glusac E, Kim YH, Hendrickson M. Reassessment of histologic parameters in the diagnosis of mycosis fungoides. Am J Surg Pathol 1995;19:1423-30]. Thus one should clarify with whom one is discussing.)

FCCL. Follicle center cell lymphoma (EORTC classification); follicle center lymphoma (REAL classification); a B-cell lymphoma exhibiting the characteristic morphologic, immunophenotypic, and cytogenetic features of its putative physiologic counterpart, the center cells of reactive (secondary) lymphoid follicles. FCCL may represent a low- or high-grade lymphoma depending on the proportion of small or large cells, respectively.

follicular lymphoma. Name recently proposed by the WHO classification for FCCL. In addition to follicular lymphoma, MZL, MCL, and CLL/SLL may also exhibit a follicular growth pattern.

$_c$Ig. Cytoplasmic immunoglobulin; detectable in formalin-fixed or frozen specimens. Only more well-differentiated B cells manufacturing immunoglobulin will have this (eg, plasmacytoma, MZL, some LBCL [immunoblastic]).

$_s$Ig. Surface/cell membrane immunoglobulin; detectable only in frozen specimens. FL, MCL, CLL/SLL, some MZLs express this.

immunoblast. Large lymphocyte similar if not indistinguishable from a centroblast; morphologically, the nucleolus may be larger and more centrally located and cytoplasm more basophilic compared with a centroblast. They may express $_c$Ig. Immunoblasts and centroblasts have distinct roles within the theoretical scheme of B-cell differentiation and function, but for diagnostic and therapeutic purposes, their counterpart lymphomas are currently consolidated as LBCL.

immunocytoma. B-cell lymphoma exhibiting the characteristic morphologic and immunophenotypic features of its putative physiologic counterpart, the immunocyte (*see* plasmacytoid). The term is used in different contexts for different clinical diseases. As a primary cutaneous lymphoma, it is classified by the EORTC as MZL (with plasmacytoid differentiation). As a systemic lymphoma, it is classified in REAL and WHO as lymphoplasmacytoid lymphoma, which correlates with the clinical features of Waldenström's macroglobulinemia.

Appendix. Cont'd

large B-cell lymphoma (LBCL). Used to classify high-grade B-cell lymphomas with a diffuse growth pattern and large cells. Previous classifications divided this into immunoblastic and centroblastic (ie, high-grade FL) types; the more descriptive term "LBCL" acknowledges our inability to reliably distinguish them (*see* "immunoblast," "centroblast," and "follicular lymphoma").

lymphocyte. Diameters of 3 to 8 μm (small), 8 to 12 μm (medium-sized), and more than 12 μm (large); adjacent keratinocyte or endothelial cell nuclei serve as an approximate reference for medium-sized cells. The lymphocytes encountered in most inflammatory skin diseases are mostly small. Plasma cells and plasmacytoid lymphocytes are larger. Large cells such as immunoblasts are few or absent in nonneoplastic infiltrates. Most T and B cells cannot be distinguished by light microscopy.

mantle cell lymphoma (MCL). B-cell lymphoma exhibiting the characteristic morphologic, immunophenotypic, and cytogenetic features of its putative physiologic counterpart, the follicle mantle zone cell.

marginal zone lymphoma (MZL). B-cell lymphoma exhibiting the characteristic morphologic, immunophenotypic, and cytogenetic features of its putative physiologic counterpart, the follicle marginal zone cell.

mucosa-associated lymphoid tissue (MALT). This concept acknowledges the extranodal lymphoid tissue (and lymphomas arising from them) normally present in mucosal sites such as the gastrointestinal tract and, analogously, the skin. A less commonly used acronym is SALT (skin-associated lymphoid tissue) (*see* "marginal zone lymphoma").

mycosis fungoides (MF). Epidermotropic T-cell lymphoma exhibiting the characteristic morphology and immunophenotypic features of its putative physiologic counterpart, the $CD4^+$ skin-homing T cell. Classically, the disease progresses from patches to plaques to tumors and erythroderma.

natural killer (NK) lymphocyte. Historically regarded as a component of nonspecific immunity, these (usually medium-sized) "large granular lymphocytes" contain cytotoxic granules. They usually label with CD56, CD57, and CD16. T-cell markers are variably expressed, but NK cells do not express T-cell receptor genes. Nevertheless, T and NK cells share certain patterns of cutaneous lymphoma, namely, angiocentric, subcutaneous panniculitic, and pleomorphic.

peripheral T-cell lymphoma. Not a specific diagnosis; refers to any T-cell lymphoma with postthymic differentiation and thus applies to all forms of CTCL except T-lymphoblastic lymphoma

plasma cell. Terminally differentiated B cell secreting immunoglobulin, also known as a plasmacyte, Marchalko plasma cell, or reticular plasma cell

plasmacytoid. Terminally differentiated B cell of the primary immune response, also known as a lymphoplasmacytoid cell, immunocyte, or lymphatic plasma cell

pleomorphic T-cell lymphoma (PTL). Rare, recently described form of CTCL composed of small and medium-sized pleomorphic lymphocytes, clinically and histologically distinct from MF.

Sézary cell. T cell with convoluted, cerebriform nucleus sometimes identified in light microscopic tissue sections and readily identifiable in peripheral blood smears and by electron microscopy; characteristic of MF but also sometimes seen in patients with nonneoplastic infiltrates (Flaxman BA, Zalazny G, Van Scott EJ. Nonspecificity of characteristic cells in mycosis fungoides. Arch Dermatol 1971;104:141-7).

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CME examination

Identification No. 802-103

Instructions for Category I CME credit appear in the front advertising section. See last page of Contents for page number.

Questions 1-30, Fung MA, Murphy MJ, Hoss DM, Grant-Kels JM. J Am Acad Dermatol 2002;46:325-57.

Directions for questions 1-30: Give single best response.

1. Regarding mycosis fungoides, each of the following is true *except*
   a. it is a proliferation of $CD4^+$ T cells.
   b. the life expectancy of a patient with limited patch or plaque disease is 10 years shorter than normal age-matched control subjects.
   c. the 5-year survival rate for a patient with tumors is 40%.
   d. Pautrier's microabscesses, if present, are the most specific histologic finding.
   e. it is more common in adults, but can occur in children.

2. A 50-year-old Jamaican woman presents with widespread cutaneous nodules, hypercalcemia, lymphadenopathy, and leukocytosis. Which of the following is the most likely diagnosis?
   a. Sézary syndrome
   b. Acute HIV infection
   c. Adult T-cell leukemia/lymphoma
   d. Cat scratch disease
   e. Hodgkin's disease

3. A 60-year-old man presents with a morbilliform eruption, fever, weight loss, generalized lymphadenopathy, and dysproteinemia. The most likely diagnosis is
   a. mycosis fungoides
   b. angioimmunoblastic T-cell lymphoma
   c. multiple myeloma
   d. measles
   e. lymphomatoid papulosis

4. A 45-year-old woman presents with a 10-year history of waxing and waning papules that crust and resolve with scarring. The lesions occur on her trunk and buttocks. A skin biopsy specimen would most likely demonstrate
   a. neutrophilic vasculitis
   b. wedge-shaped diffuse infiltrate with $CD30^+$ large atypical cells
   c. psoriasiform epidermal hyperplasia with neutrophils in the stratum corneum
   d. loss of dermal elastic tissue with wreathlike giant cells
   e. numerous plasma cells with amyloid deposition

5. $CD30^+$ lymphocytes are an integral part of each of the following *except*
   a. cutaneous Hodgkin's disease
   b. lymphomatoid papulosis
   c. (anaplastic) large-cell lymphoma
   d. marginal zone lymphoma

6. Appropriate therapy for limited patch/plaque mycosis fungoides includes each of the following *except*
   a. topical nitrogen mustard
   b. PUVA
   c. topical corticosteroids
   d. UVB
   e. combination chemotherapy

7. Immunohistochemical studies to determine clonality in a patient with suspected B-cell lymphoma is most likely to show
   a. κ to λ ratio greater than 5:1
   b. κ to λ ratio of about 2:1
   c. κ to λ ratio less than 5:1
   d. κ to λ ratio greater than 2:1
   e. none of the above

8. Gene rearrangement analysis using the Southern blot technique can be performed on
   a. fresh-frozen tissue
   b. ethyl alcohol–fixed tissue
   c. formalin-fixed tissue
   d. xylene-fixed tissue
   e. all of the above

9. A patient with histologic findings of a sparse to moderate dermal infiltrate is suspected of having a cutaneous lymphoma. Which of the following is the most appropriate next step in establishing the diagnosis from the specimen?
   a. Polymerase chain reaction
   b. Flow cytometry

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c. Southern blot analysis
d. Immunohistochemical studies
e. None of the above

10. Which of the following eruptions has occasionally demonstrated clonal T-cell receptor gene rearrangement?
a. Lichen sclerosus
b. Pigmented purpura
c. Lichen planus
d. Pityriasis lichenoides
e. All of the above

11. Diminished survival of patients with cutaneous T-cell lymphoma who have mycosis fungoides or Sézary syndrome is associated with
a. elevated levels of serum lactate dehydrogenase
b. age younger than 50 years at time of diagnosis
c. absence of circulating T-cell clone
d. male sex
e. elevated erythrocyte sedimentation rate

12. A patient infected with human T-cell lymphotropic virus type I is at risk for the development of
a. adult T-cell leukemia/lymphoma
b. angiocentric lymphoma
c. large T-cell lymphoma
d. angioimmunoblastic T-cell lymphoma
e. Lennert's lymphoma

13. Lymphomatoid granulomatosis is most likely to involve the
a. lungs
b. skin
c. liver
d. brain
e. colon

14. Diminished survival of patients with primary cutaneous lymphomas other than mycosis fungoides or Sézary syndrome is associated with
a. elevated levels of serum lactate dehydrogenase
b. age younger than 50 years at time of diagnosis
c. absence of circulating T-cell clone
d. male sex
e. elevated erythrocyte sedimentation rate

15. Lymphocyte clonality may be demonstrated by each of the following *except*
a. light microscopy
b. immunohistochemistry
c. gene rearrangement analysis
d. flow cytometry

16. Which of the following statements regarding immunohistochemistry is *false*?
a. It requires fresh-frozen tissue for analysis.
b. It can distinguish between lymphoid and nonlymphoid cells.
c. It can distinguish between B, T, and natural killer cells.
d. It can distinguish between subsets of T cells.
e. It can distinguish between subsets of B cells.

17. Gene rearrangement analysis is useful in demonstrating each of the following *except*
a. T-cell clonality
b. B-cell clonality
c. natural killer–cell clonality
d. lymphocyte clonality in mycosis fungoides

18. Which of the following statements about polymerase chain reaction analysis of lymphocyte clonality is *true*?
a. It requires fresh-frozen tissue.
b. It is less sensitive than Southern blot analysis.
c. It amplifies specific RNA sequences.
d. It utilizes nucleotide primers.

19. Southern blot analysis has a sensitivity of
a. 0.1%-1%
b. 1%-5%
c. 5%-10%
d. 10%-20%
e. >20%

20. In cutaneous lymphomas, gene rearrangement analysis by polymerase chain reaction is useful in each of the following *except*
a. diagnosing initial disease
b. distinguishing histologic subtypes of lymphomas
c. monitoring response to therapy
d. detecting minimal residual disease

21. Clonal T-cell receptor gene rearrangements have been demonstrated in each of the following *except*
a. lymphomatoid papulosis
b. pityriasis rosea
c. pityriasis lichenoides
d. lichen planus
e. adult T-cell leukemia/lymphoma

22. Which of the following is a common complication of therapy with topical nitrogen mustard?
a. Allergic contact dermatitis
b. Bullous reaction
c. Telangiectasia
d. Hyperpigmentation
e. Hypopigmentation

23. Which of the following is a common complication of therapy with topical carmustine (BCNU)?
a. Allergic contact dermatitis
b. Bullous reaction
c. Telangiectasia
d. Hyperpigmentation
e. Hypopigmentation

24. Which of the following has been described in association with denileukin diftitox therapy?
a. Depression
b. Hypertriglyceridemia
c. Aplastic anemia
d. Vascular leak syndrome
e. Idiopathic thrombocytopenic purpura

25. Determination of which parameter is most important for determining prognosis in cutaneous lymphoma?
a. Primary cutaneous versus secondary cutaneous

b. B- versus T-cell phenotype
c. T- versus natural killer–cell phenotype
d. Degree of anaplasia
e. Presence or absence of a circulating clonal lymphocyte proliferation

26. The most common form of primary cutaneous lymphoma encountered by dermatologists is
a. marginal zone lymphoma
b. low-grade follicular lymphoma
c. Hodgkin's disease
d. Sézary syndrome
e. mycosis fungoides

27. The recommended length of clinical follow-up before establishing a diagnosis of *primary* cutaneous lymphoma is
a. 3 months
b. 6 months
c. 12 months
d. 24 months
e. 5 years

28. Bone marrow biopsy is not routinely recommended for patients with
a. angiocentric natural killer cell lymphoma
b. mantle cell lymphoma
c. lymphoblastic lymphoma
d. large T-cell lymphoma
e. mycosis fungoides

29. Which disorder often presents with neurologic abnormalities, including dementia or speech, sensory, or visual abnormalities?
a. Marginal zone lymphoma
b. Intravascular lymphoma
c. Subcutaneous panniculitis–like T-cell lymphoma
d. Angioimmunoblastic T-cell lymphoma
e. Erythrodermic mycosis fungoides

30. You submit a 4-mm punch (trephine) biopsy specimen. Later you receive the pathologist's report indicating "atypical lymphoid infiltrate." Additional testing that may be performed on the formalin-fixed specimen you have already submitted includes each of the following *except*
a. Southern blot gene rearrangement analysis for B- or T-cell clonality
b. Polymerase chain reaction–based gene rearrangement analysis for B- or T-cell clonality
c. Immunohistochemical studies for immunophenotype analysis
d. Immunohistochemical studies for B-cell clonality
e. Immunohistochemical studies for CD30 (Ki-1)