1 Patterns of Lymphohistiocytic Reaction in Skin: An Approach to Cutaneous Lymphohematopoietic Infiltrate Using Histologic Patterns and Immunostains

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Introduction

It is helpful to think of cutaneous lymphomas in the context of their relationship to normal skin structures. Here, we proffer an approach using guidelines based on the usual patterns seen in reactive histology of skin with lymphocytic and histiocytic reactions. There is increasing evidence that neoplastic histomorphologic patterns are superimposed on normal physiologic patterns. See Chap. 2 on this evidence. Morphologic and immunophenotypic reactions show a relatively consistent pattern.

Many advances have been made through the cooperation of international medical groups, such as the European Organization for Research and Treatment of Cancer (EORTC) and the World Health Organization (WHO), and their joint classification of primary cutaneous lymphomas (Willemze et al. 2005) (partly shown in Table 1.1). Thanks to this excellent effort by these dedicated groups, a common language is now spoken by dermatopathologists, hematopathologists, and clinicians in diagnosing and treating cutaneous lymphomas. Continuous progress especially in the application of molecular pathology brought forth new information and facilitated better understanding, not only of neoplastic but also of nonneoplastic cutaneous lymphoid infiltrates. Foremost is the recognition that cutaneous lymphomas are different from the similarly named nodal or systemic lymphomas and have to be approached and treated differently.

Extranodal lymphomas, especially those arising from the most visible organ, i.e., the skin, present, for the most part a different biology, pathogenesis, and, for the common types, a better response to therapy. In addition, access to skin lesions is relatively easy compared to nodal and other systemic lesions. Hence, work-up of a suspected lump or growth almost always involves a biopsy. The histology may be nonlymphoid or a lymphohematopoietic process. Rarely, the monomorphic infiltrate can resemble lymphoma though upon further comprehensive analysis it is discovered to be a poorly differentiated sarcoma, leukemia, carcinoma, or melanoma.

Hence, this book addresses the issue of approaching a biopsy with an open viewpoint that the lesion confronted could be lymphoid or nonlymphoid, neoplastic, dysplastic (but not frankly neoplastic), or reactive in nature. The first step in analyzing the biopsy begins with the microscope. Because most books in this subject organize the topics into known diseases or lymphoproliferations, we chose to differ in

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Table 1.1 Overview of nonneoplastic and neoplastic cutaneous lymphohematopoietic infiltrates

Nonneoplastic	Neoplastic
Reactive epidermotropic and lichenoid dermatitis	*Cutaneous T-cell and NK-cell lymphomas*
Langerhans cell hyperplastic vesicles, SD	Mycosis fungoides (MF)
Epidermotropic T-cell pseudolymphomas	MF variants and subtypes
Pseudolymphomatous folliculitis/idiopathic FM	Folliculotropic MF
"Spongiotic dermatitides (SD)"/lymphomatoid keratosis	Pagetoid reticulosis
Benign granulomatous dermatitis/dyscrasia	Granulomatous slack skin
Inflammatory vitiligo/hypopigmented T-cell dyscrasia	Hypopigmented MF
Syringolymphoid T-cell hyperplasia/dyscrasia	Syringolymphoid MF
Benign erythroderma/T-cell lymphocytosis of uncertain significance	Sézary syndrome
Benign lymphocytosis/ T-cell pseudolymphomas	Adult T-cell leukemia/lymphoma
CD30 pseudolymphomas	Cutaneous CD30+ lymphoproliferative disorders
Nonclonal "regressing histiocytosis"	Anaplastic large cell lymphoma
Scabies, other CD30(+) infections, PLEVA	Lymphomatoid papulosis
Lupus profundus and other reactive panniculitis	Subcutaneous panniculitis-like T-cell lymphoma (SPCTL)
Reactive drug-induced/idiopathic vasculitis	Extranodal NK/T-cell lymphoma, nasal type
Nodular T-cell pseudolymphomas	Cutaneous peripheral T-cell lymphoma (large cell), unspecified
Pityriasis lichenoides et varioliformis acuta (PLEVA) and chronica (PLC)	Cutaneous aggressive epidermotropic CD8+ T-cell lymphoma
Spongiosis and reactive panniculitis	Cutaneous γ/δ T-cell lymphoma
Solitary T-cell nodules uncertain significance	Cutaneous small-/medium-sized lymphomas (CD8, CD4)
Germinal center hyperplasia	*Cutaneous B-cell lymphomas*
Cutaneous B-cell lymphoid hyperplasia	Primary cutaneous marginal zone B-cell lymphoma
(B-cell pseudolymphomas)	Primary cutaneous follicle center lymphoma
Drug-induced hyperplasia (i.e., phenytoin)	Primary cutaneous diffuse large B-cell lymphoma, leg type
Solitary B-cell pseudolymphomas	Primary cutaneous diffuse large B-cell lymphoma, others
Granulomatous dermatitis	Lymphomatoid granulomatosis
Cutaneous IgG4 plasmacytosis	Plasmacytoma
Intravascular (intralymphatic) histiocytosis	Intravascular lymphoma
Sinus histiocytosis with massive lymphadenopathy	Hodgkin lymphoma
Langerhans cell hyperplasia	Langerhans cell histiocytosis
Immature extramedullary hematopoiesis	*Cutaneous plasmacytoid dendritic leukemia*
	Cutaneous granulocytic sarcoma
	Mastocytosis/Mast cell sarcoma
	Lymphoblastic T- or B-cell lymphoma

FM follicular mucinosis

proffering an approach based on morphologic *patterns*. In this way, the microscopic findings provide the point of departure to seek the most precise diagnosis based first on tissue patterns, then on cytomorphology, immunophenotypic results, and when necessary molecular genetic analysis. Furthermore, we subscribe to the state-of-the-art cutaneous lymphoma consensus classifications and atypical lymphoproliferations (Cerroni et al. 2009; Magro et al. 1997, 2003; Magro and Crowson 1996; Swerdlow et al. 2008; Isaacson and Norton 1994). See Table 1.1 for the overview of benign and malignant cutaneous lymphohematopoietic infiltrates listing topics covered in this book.

Synonyms

Cutaneous lymphoid hyperplasia (Lymphadenosis benigna cutis, Lymphocytoma cutis, Pseudolymphoma)

Granulocytic sarcoma (leukemia cutis, myeloid sarcoma, myelomonocytic sarcoma, extramedullary leukemic skin infiltrate)

Definitions

Cutaneous lymphoid hyperplasia (CLH) with band-like and perivascular pattern is a reactive pattern of the skin that histologically resemble mycosis fungoides.

Cutaneous lymphoid hyperplasia with nodular pattern ("nodular pattern of cutaneous lymphoid hyperplasia") is a reactive histologic pattern in skin characterized by solitary or localized nodules predominantly in the dermis that clinically appear as a reddish to violaceous lump. The presence of germinal centers forming most nodules indicates a B-cell type. It is our experience that dermal compact nodules often mark as a T-cell type of nodular cutaneous lymphoid hyperplasia instead of a B-cell type.

Pseudolymphomas of skin are reactive proliferations that clinically or histologically resemble cutaneous lymphomas (Cerroni et al. 2009; Cerroni 2006). Pseudolymphoma is not a specific diagnosis and encompasses cutaneous lymphoid hyperplasia and drug-induced or infection-induced skin lymphoid lesions of varied pathogenesis, appearance, and clinical behaviors. Although progression from a reactive process to a lymphoma is not a usual course of pseudolymphomas, lymphomas in preexisting hyperplasia do sometimes occur (Bergman 2010). Hence, recurrent or persistent lesions with an appearance suggestive of lymphoma require careful follow-up to rule out progression to malignancy. See Chaps. 5, 7, and 8 on expanded discussion of pseudolymphomas.

Atypical cutaneous lymphoid hyperplasias may include abnormal, disorganized, or transformed germinal centers (Kojima et al. 2010a, b) associated with atypical cells or as dense dermal or subcutaneous lymphoid diffuse infiltrates with atypical cells. Lesions are usually persistent or recurrent over several years.

Cutaneous lymphomas are a diverse group of heterogeneous entities arising from malignant lymphoproliferation of either T-cell, B-cell, or natural killer-cell lineage, which primarily originate, present, or remain confined to the skin without detectable extracutaneous manifestations at diagnosis.

Epidemiology

Primary cutaneous lymphomas have an estimated annual incidence of 1.0–1.5/100,000 and are the second most common group of extranodal lymphomas. Despite their relative low frequency, there has been an increasing incidence of cutaneous lymphomas in the United States from 5 to 13 per million person-years over 25 years reported in 2005 (SEER data) (Bradford et al. 2009). The incidence of cutaneous T-cell lymphomas (CTCL) is 3–9 per million, and like all cutaneous lymphomas, this incidence appears to be increasing both in North America and in Europe (Criscione and Weinstock 2007; Jenni et al. 2011). Mycosis fungoides (MF) and Sézary syndrome (SS) represent the most common cutaneous lymphomas and account for 4.1 per million person-years (Bradford et al. 2009). Although MF is an indolent lymphoma, histologic and clinical progression often occurs over time. Large cell transformation of MF occurs in up to 7 % of early clinical stages but up to 23 % in advanced clinical stages of MF (Lai et al. 2012). Diagnosis of these rare cutaneous T-cell lymphomas which vary from focally epidermotropic early MF to non-epidermotropic dense dermal infiltrates is challenging.

Cutaneous Lymphoid Hyperplasia

Although there is no exact data on the actual incidence of CLH or cutaneous pseudolymphoma, the frequency of diagnosis of cutaneous lymphoid hyperplasia in premodern pathology practice is higher than the frequency of diagnosis of cutaneous lymphoma. In an early seminal study comparing 225 skin biopsies for benign and malignant lymphoid infiltrates, benign diagnoses accounted for 61 % and malignant lymphoid

infiltrates comprised 39 % (Caro 1978; Caro and Helwig 1969).

In our current referral consultation practice, however, pseudolymphomas comprise about 30 % and lymphomas 60 %, with myelomonocytic/non-hematopoietic diagnosis comprising about 10 %. B-cell pseudolymphomas account for about 5 % (defined as having 70 % or more of B-cell nodules), T-cell pseudolymphoma account for about 10 % (defined as a band or nodular infiltrate with 90 % or more T cells), and mixed T- and B-cell pseudolymphomas account for about 15 % (with mixed T cells and B cells, usually of approximately equal proportion plus a range that does not fit the defined brackets for either previous types).

Borrelia-associated lymphoid hyperplasia is uncommon, occurring in about 1 % of cases reported in Europe (Colli et al. 2004) and in North America; a variety of skin infiltrative patterns is also observed (Lipsker 2007). Drug-induced pseudolymphoma is an equally rare condition with more than 100 individual cases reported in the literature worldwide, and may easily be mistaken for lymphoma if a drug etiology is not uncovered. When associated with systemic symptoms and hypersensitivity such as those typical for a drug reaction with systemic symptoms (DRESS), mortality is reported in up to 10 % of patients (Bocquet et al. 1996).

Cutaneous lymphoid hyperplasia (CLH) is generally classified according to clinicopathologic entities or placed into broad spectrums of B-cell or T-cell predominance or co-dominance (Bergman et al. 2011). The predominant immunologic type usually can be inferred from the histopathologic pattern supplemented by immunohistochemistry, and in correlation with molecular genetic analysis using appropriate T-cell antigen receptor or immunoglobulin, gene primers and PCR can usually distinguish cutaneous lymphoid hyperplasia from cutaneous lymphoma. A recent study suggests that using a panel of cytotoxic markers, the expression of granulysin, may be differentially expressed more in CLH more than in cutaneous large B-cell lymphoma (Furudate et al. 2013). Granulysin or granzyme B is a cytolytic substance released by cytotoxic T cells (CD8+) during 3–5 days after their activation.

In cases with mild to moderately atypical cells, a clonal population that correlates clinically with a recurrent or persistent mass after repeated biopsies and clinical follow-up usually indicates a malignancy. On the other hand, the presence of clusters of plasma cells or eosinophils along with reactive histiocytes in association with "top-heavy" nodules, or spongiotic epidermis, is often indicative of a reactive proliferation with defined and specific exceptions. Care must be taken with cases that present with benign-looking germinal centers because this is a common pattern associated with lymphomas arising from the marginal zone (Arai et al. 2005; Baldassano et al. 1999).

Clinical evidence of progression is probably the ultimate determinant of whether heavy, multinodular cutaneous lymphoid infiltrates, with or without the presence of a clonal B- or T-cell population, have become a cutaneous lymphoma (Ceballos et al. 2002).

Processing of the Skin Biopsy

It is essential to obtain as much information as possible from the skin biopsy. Because of the usual small size, often a punch biopsy, we recommend immediate splitting of the biopsy into separate parts for conventional histology and possible future studies requiring unfixed cryopreserved tissue. This is especially important for cutaneous lymphomas for which immunohistochemistry, immunofluorescence, gene rearrangement, and other molecular genetic studies require optimal preservation of RNA, DNA, and cell surface proteins. In academic centers, there may be opportunities for cytogenetics, tissue culture, flow cytometry, and transplantation to immunodeficient mice. Thus, the protocol for processing skin biopsies will vary according to your practice. For dermatologists, it is obviously of great importance to establish a well-rehearsed routine with your pathologists and research associates according to your goals. For punch biopsies, we find it practical to place the skin surface down on a cutting surface and bisect the specimen with a sterile

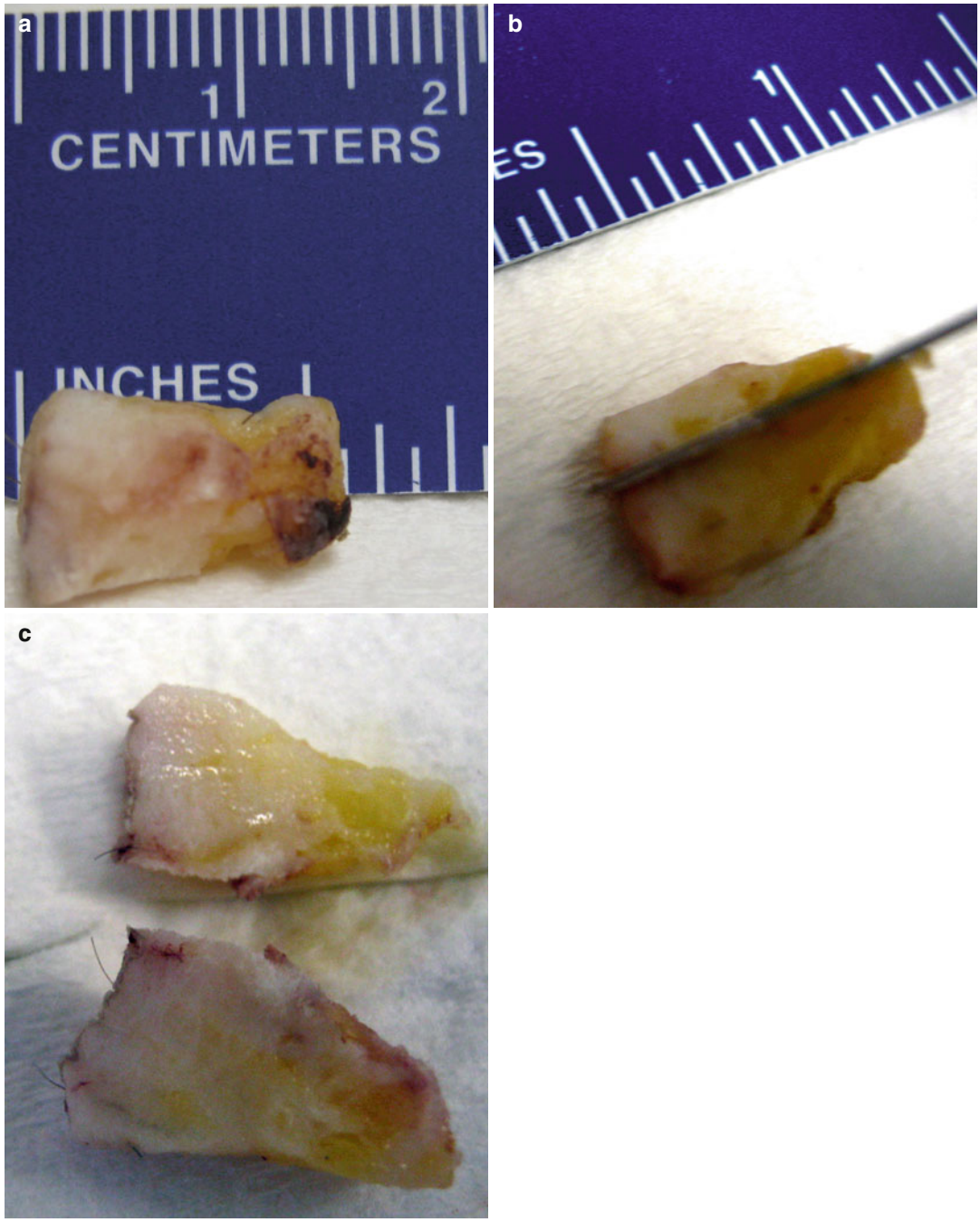

Fig. 1.1 (**a**) Gross picture of a 6 mm punch biopsy and (**b**) its bisection. (**c**) Cut section with yellow fat and whitish dermis (Courtesy of George Gibbons, Dermatopathologist, Dermpath Diagnostics, Tampa FL)

sharp scalpel or razor blade along the longitudinal axis (Fig. 1.1). One-half of the specimen can then be placed immediately into fixative, and the other one-half placed into sterile saline or on a sterile saline-soaked gauze and sent to the laboratory. With improved immunohistochemical methods

including antigen retrieval and virtual flow immunohistochemistry (see Chap. 4 for this technology), much information can be available from fixed tissue. Ten percent buffered formalin is adequate for most studies. Optimal morphology and immunohistochemistry is gleaned from 4 % paraformaldehyde fixation (Muramoto and Kadin 1987).

Optimal Specimen for Work-Up of Cutaneous Lymphoid Infiltrates

Since a skin biopsy is often submitted without prior knowledge of the type of infiltrate and since epithelial and melanocytic proliferations are the usual considerations, specimens are obtained in the most common and convenient manner, either by shave, punch, or excision biopsy. Shave biopsies, if scalloped or deep to obtain deeper dermal or subcutaneous tissues, can offer a suitable specimen. However, the common thin shave biopsies we receive with associated lymphoid lesions generally do not provide adequate information on deeper dermal or subcutaneous areas, so that eccrino-syringotropic or subcutaneous panniculitic lesions are not recognizable.

If a lymphoid lesion is strongly suspected, superficial shave biopsies should be avoided. Many of our cases submitted for molecular assays from shave biopsies fail to provide adequate DNA for clonality analysis (see Chap. 4 on increased false-negative or oligoclonal results that are seen from thin shave biopsies). As a rule, a lymphoid infiltrate section is subjected to a battery of ancillary tests including multiple step sections for a number of immunoperoxidase stains plus DNA analysis for T- or B-cell clonality. If a molecular genetic assay is performed on the tissue section or block after sectioning for immunohistochemistry, test failures due to inadequate DNA may result. To avoid this, a routine stain and immediate submission of the tissue for molecular IgH or T-cell receptor gene rearrangement assays are recommended. This has worked in our practice with the caveat that any additional immunohistochemistry that may be needed to classify the lesion will be delayed.

In centers equipped with the ability to process fresh tissue using tissue culture media, additional information can be obtained via flow cytometry analysis, especially useful in clonal light chain analysis or T-cell aberrancy analysis for B- and T-cell lymphoproliferations, respectively. Caution is advised in interpreting the results of flow cytometry without histologic correlation, since flow cytometry analysis requires tissue disaggregation and the neoplastic large cell population may be "lost" or obscured by the more numerous reactive small cell population. Interpreting the results of flow cytometry as negative for lymphoma must be correlated with the morphology or immunohistochemistry. This approach is similar to the work-up for nodal lymphomas or leukemias, using a multiparameter approach, as the best way to arrive at the most accurate diagnosis.

Morphologic Approach

As in evaluations of other dermatologic disorders, the first step in the pathologic assessment is to obtain an overview of the specimen using a low-power (2× or 4×) objective lens. Note whether the lymphoid infiltrate is compact or dispersed and involves the epidermis, dermis, and/or subcutaneous tissues. It is important to note the presence of reactive germinal centers of altered follicles in B-cell disorders, e.g., marginal zone lymphoma. Note if there are foreign bodies or pathogens, such as mites in scabies.

In biopsies with germinal centers, it is important to note if the germinal centers have a normal polarized appearance with a paler germinal center composed of mixed centrocytes and centroblasts and a rim of smaller perifollicular lymphocytes representing the mantle zone. If the germinal centers are transformed, simulating progressive transformation of germinal centers, or else lysed, disorganized, or admixed with other atypical cells or otherwise with expanded mantle or marginal zone lymphocytes, then these atypical findings

call for a higher index of suspicion for lymphoma, prompting further ancillary work-up to distinguish B-cell lymphoma or transformation of a B-cell cutaneous lymphoid hyperplasia.

Mantle cell lymphoma is exceedingly rare as primary skin lymphoma but cutaneous involvement by nodal follicle center or marginal zone lymphoma is relatively frequent, if there are corresponding known nodal follicular or marginal zone lymphomas. If primary cutaneous lymphoma is suspected, the following histologic features would be indicative of a primary cutaneous marginal zone lymphoma: normal or colonized germinal centers, along with expanded marginal zones, composed of small- and medium-sized lymphocytes with a moderate amount of cytoplasm, centrocyte-like round to irregular nuclei, and admixed plasma cells. Indeed, many cutaneous lymphoid hyperplasias diagnosed in the past before the era of more sensitive immunohistochemistry or molecular gene rearrangement assays turned out to be cutaneous marginal zone lymphomas. (Please see Chap. 3 for differential diagnosis of primary cutaneous B-cell lymphomas.)

Using medium-power 10× and 20× objectives, one can appreciate if adnexa and blood vessels are affected and whether or not there is an interface pattern at the dermal-epidermal junction. Pautrier's microabscesses diagnostic of MF can be suspected at medium-power magnification. A general impression can also be gained of the presence or absence of inflammatory cells, e.g., neutrophils, eosinophils, plasma cells, and macrophages. Necrosis of keratinocytes and blood vessels can be determined.

High magnification with 40–60× objectives is required to note nuclear conformation, irregularities or convolutions, presence or absence of nucleoli and their prominence, presence of mitotic figures, and apoptotic bodies or karyorrhexis. Oil immersion lens of 60–100× magnification, if available, provide the clearest view to assess hyperconvoluted or cerebriform nuclei. Nuclear convolutions are especially noteworthy in assessing cutaneous T-cell lymphomas, e.g., mycosis fungoides and Sézary syndrome. It is often necessary to confirm the presence of three or more tumor cells with nuclear irregularities comprising a Pautrier's microabscess and distinguish them from Langerhans cells which also have nuclear convolutions but more elongated nuclei and pale staining cytoplasm (for illustrations and further details, see Chap. 6). Prominent nucleoli and mitotic figures are characteristic of CD30+ cutaneous lymphoproliferative disorders, as well as the presence of more than 90 % immunoblasts or centroblasts typical for the leg type of diffuse large B-cell lymphoma. Karyorrhexis is a feature of subcutaneous and gamma-delta T-cell lymphoma that may distinguish them from autoimmune disorders involving the skin, e.g., lupus profundus.

As in melanoma evaluation, immunohistochemistry can help to identify tumor cells that may otherwise escape your attention. For example, stains for CD3 and TCR beta f1 often outline the nuclear convolutions of tumor cells in mycosis fungoides/Sézary syndrome, helping to distinguish them from reactive lymphocytes. Immunohistochemical enumeration of reactive cells can also be of importance for prognosis of CTCL. We recently reported that tumor progression from early-stage (I–IIA) CD4+ MF is significantly correlated with <20 % CD8+ cells in the dermal infiltrate (Vonderheid et al. 2014).

Normal Skin Histology

This low-power view shows a typical histology of skin showing epidermis, hair follicles, and sweat and sebaceous glands (Fig. 1.2).

Epidermis

The epidermis consists of four layers (five in the soles and palms) starting from the most superficial or outward layer: a cornified layer (stratum corneum), a granular layer (stratum granulosum) in which keratinocytes lose their nuclei and their cytoplasm appears granular, a spinous layer (stratum spinosum), and a basal/germinal

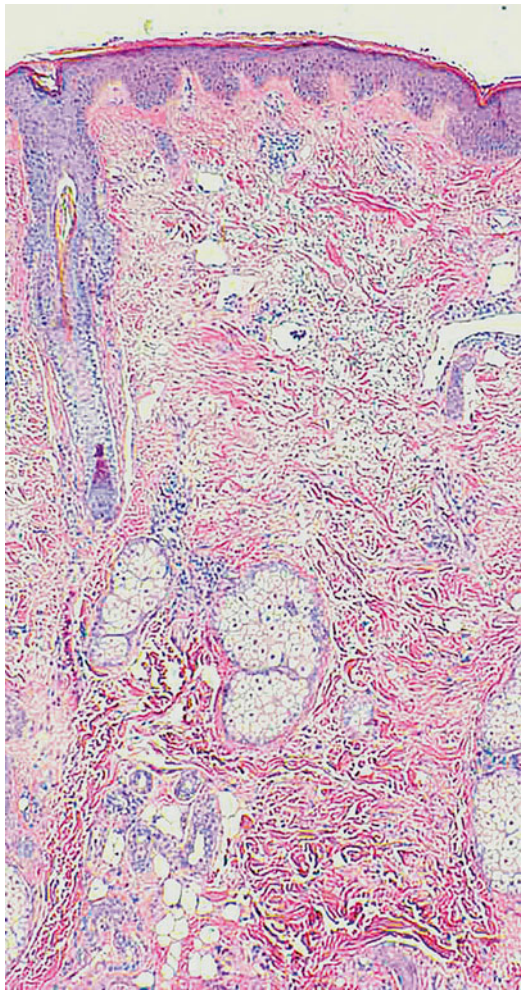

Fig. 1.2 Low power of normal skin showing epidermis with rete ridges and hair follicle on left with sebaceous and eccrine glands below, some endothelial vessels with minimal lymphoid elements

layer (stratum basale/germinativum) composed mainly of proliferating and nonproliferating keratinocytes. In CTCL, lymphocytes initially line up in the basal layer of the epidermis (lymphocyte tagging) and are often surrounded by a clear space (halo) (Fig. 1.3). Clusters of three or more lymphocytes within the epidermis comprise a Pautrier's microabscess which is a diagnostic feature of MF/SS (Fig. 1.4). In CTCL, tumor cells are CD4+ in >90 % of cases. It should be appreciated that CD8+ cells are also commonly found in the epidermis in CTCL. See Chap. 6 for discussion of neoplastic epidermotropic patterns.

Keratinocytes comprise the predominant cell type in the epidermis, the outermost layer of the skin, constituting 90 % of the cells found there.

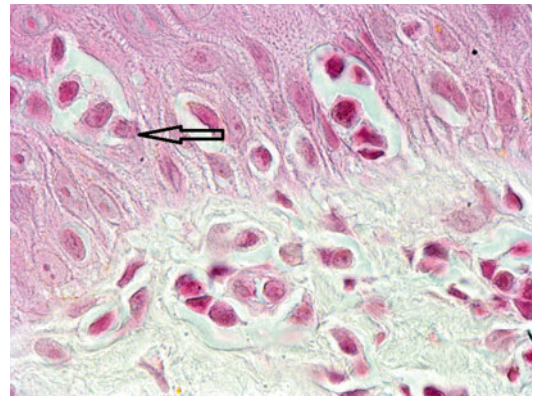

Fig. 1.4 Early Pautrier's or Darier's nest with six atypical lymphocytes (*arrow*) surrounding a Langerhans cell

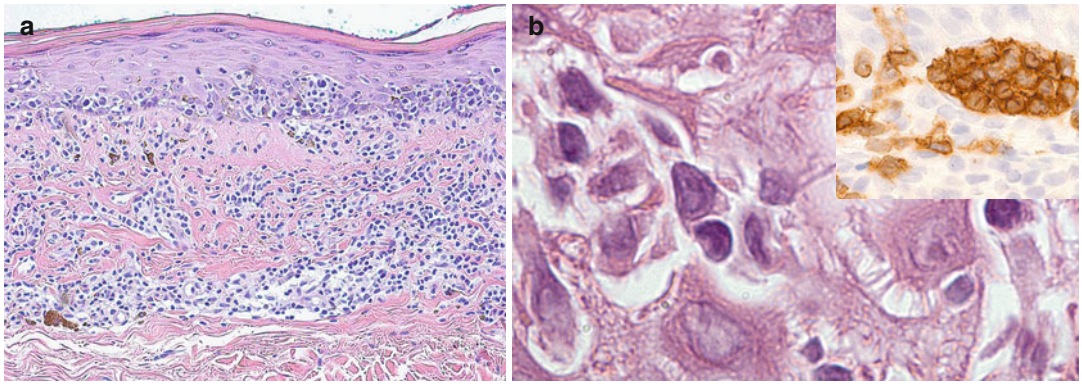

Fig. 1.3 (**a**) Typical mycosis fungoides basal layer localization of haloed atypical lymphocytes with Pautrier's microabscesses. (**b**) Oil power view of cerebriform cells and of *inset* CD3 stain, highlighting the nuclear hyperconvolutions

The primary function of keratinocytes is the formation of a barrier against environmental damage such as pathogens (bacteria, fungi, parasites, viruses), heat, UV radiation, and water loss. Once pathogens start to invade the upper layers of the epidermis, keratinocytes can react with the production of proinflammatory mediators and in particular chemokines such as CXCL10 and CCL2 which attract leukocytes to the site of pathogen invasion. Keratinocytes also produce stem cell factor (SCF) which stimulate the SCF receptor (also called cKIT or CD117) on the surface of melanoblasts and melanocytes. The cytolytic effect of junctional CD8 T cells against these receptors or against keratinocytes, leading to cell death, is implicated in the pathogenesis of hypopigmented MF (Singh et al. 2006) (Fig. 1.5). In turn, keratinocyte growth and differentiation can be affected by lymphocyte-derived cytokines, in particular IL-22 which we have found to promote pseudoepitheliomatous keratinocyte hyperplasia, a condition mimicking squamous cell carcinoma (Guitart et al. 2013).

Antigen presenting cells within the epidermis are known as Langerhans cells (LC). LC have abundant pale staining cytoplasm and an elongated convoluted nucleus with clear nucleoplasm and inconspicuous nucleoli and stain readily with S100 antibody. When hyperplastic and forming vesicles, they must be distinguished from tumor cells in MF/SS which have only a

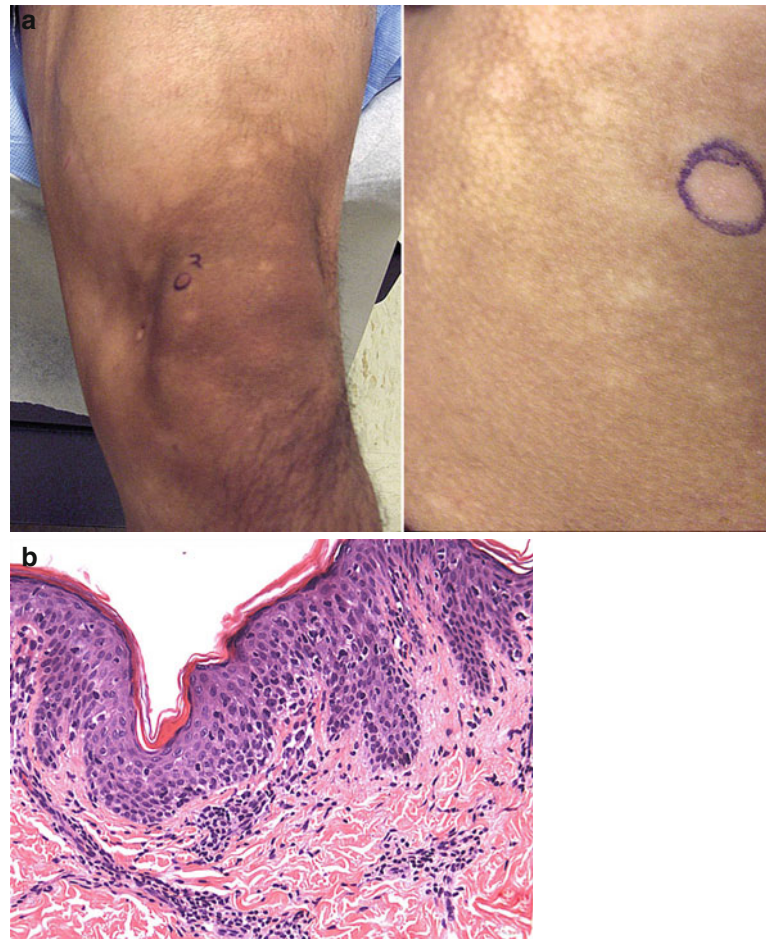

Fig. 1.5 (**a**) Hypopigmented MF in a young Asian, knee and elbow. (**b**) Histopathology (Courtesy of Neil Fenske, Chair Dermatology and Frank Glass, University of South Florida)

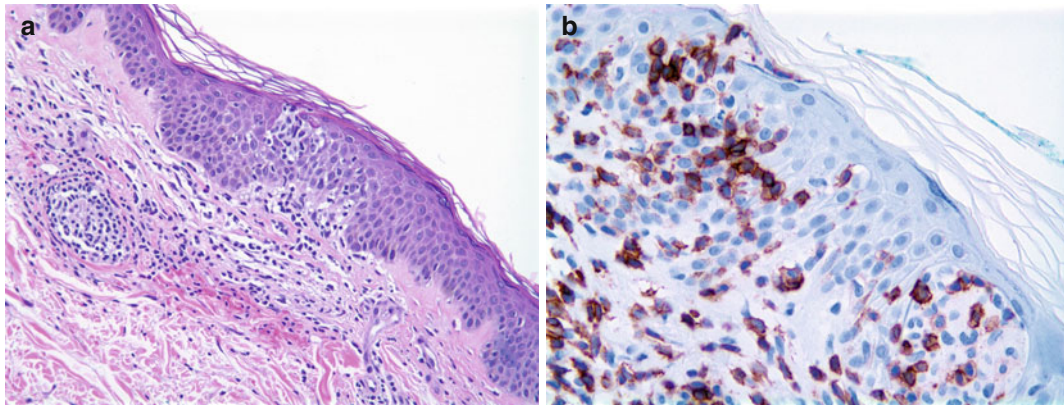

Fig. 1.6 (**a**) Langerhans cell hyperplastic vesicle in contact dermatitis. (**b**) CD3 staining of epidermotropic lymphocytes is largely absent in vesicle with Langerhans cell hyperplasia

narrow rim of cytoplasm, dark and sometimes mottled nucleoplasm, and occasional nucleoli (Fig. 1.6). See Chap. 5 for discussion of reactive lichenoid and epidermotropic disorders.

Intercellular edema or spongiosis is more common in reactive processes but can occur in CTCL and does not discount a diagnosis of CTCL. Necrotic keratinocytes can be found exceptionally in lichenoid CTCL (Guitart et al. 1997) but are more common in interface dermatitides, e.g., PLEVA and lichen planus.

Dermis

The dermis is the main compartment involved in most nodular patterns seen in subtypes of cutaneous B-cell lymphomas (Fig. 1.7). See Chap. 9 for discussion of neoplastic nodular B-cell patterns. The dermis is the site of the major tumor T-cell infiltrate in plaque and tumor stages of mycosis fungoides and in anaplastic large cell lymphoma. The dermis is also the location of most T-cell lymphomas with a nodular dermal pattern such as primary cutaneous small-medium T-cell lymphoma and angioimmunoblastic and extranodal NK/T-cell lymphomas. See Chap. 10 for discussion of T-cell lymphomas with nodular pattern, including transformed MF. Dermal infiltration is uncharacteristic of SPTCL but is common in gamma-delta T-cell lymphoma and other cytotoxic lymphomas such as extranodal NK/T-cell lymphomas.

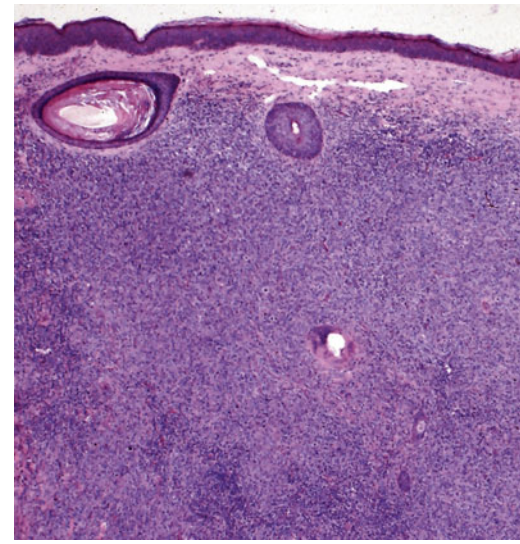

Fig. 1.7 Cutaneous B-cell lymphoma with dermal nodular and sparing of grenz zone pattern

Subcutaneous Tissue

Fat necrosis and rimming of fat cells by atypical neoplastic cells is characteristic of SPTCL and some cases of gamma-delta T-cell lymphoma. Subcutaneous fat is also infiltrated by lymphocytes in lupus, but fat necrosis and rimming of fat cells by atypical pleomorphic lymphocytes is unusual. The involvement of fat is seen in anaplastic large cell lymphoma, large cell transformation of MF, and precursor blastic tumors of either B- or T-cell type as well (Fig. 1.8).

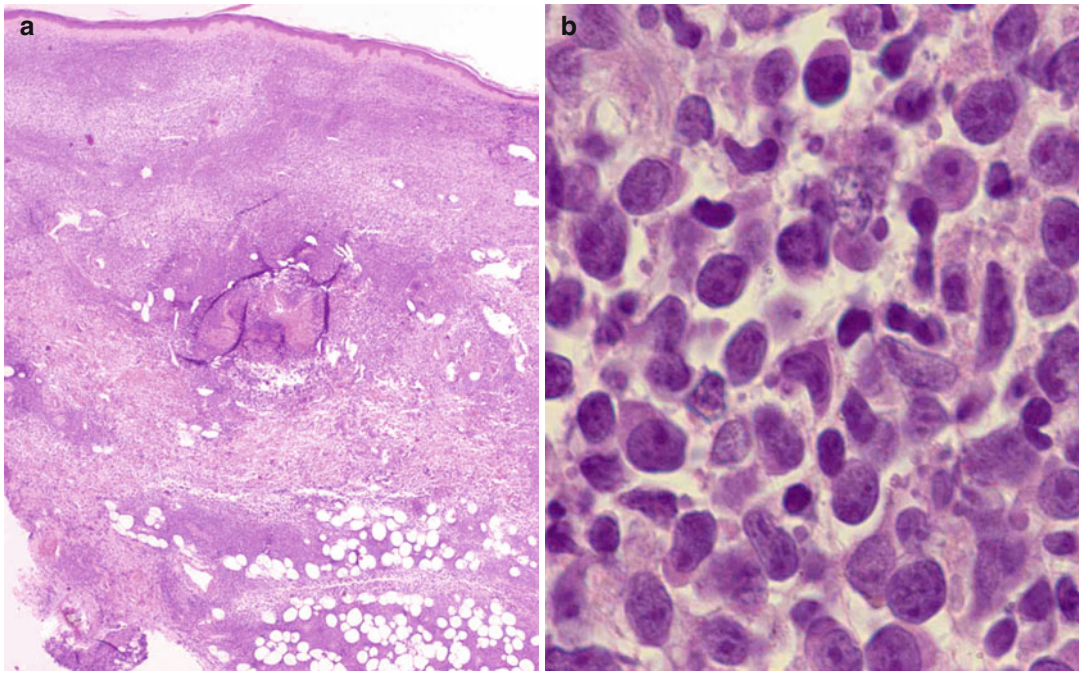

Fig. 1.8 (**a**) Precursor B-cell lymphoblastic lymphoma with deep fat involvement. (**b**) Oil magnification, with lymphoblasts with fine blastic chromatin and abnormal mitosis

Septal panniculitis is more common in reactive or infectious process (erythema nodosum or induratum), and nodular or mixed nodular patterns with minimal septal fat involvement are more common in SPTCL and fat involvement of gamma-delta T-cell lymphoma. See Chap. 11 for further discussion of subcutaneous neoplastic and reactive patterns.

Patterns of Lymphoid Reactions in Skin

Epidermotropic

Lichenoid Pattern

Lichenoid pattern is a band-like pattern with lymphocytes closely apposed to the epidermis with minimal epidermal vacuolar changes. It is a common pattern seen in both reactive and malignant processes. It is often associated with varying upper dermal perivascular lymphoid pattern and may be associated or delineated from an interface pattern which shows prominent vacuolar changes (Guitart et al. 1997; Magro and Crowson 2000; Oliver et al. 1989). Discussion of epidermotropic as well as dermotropic changes in association with reactive lichenoid patterns is in Chaps. 5 and 8, respectively.

Minimal vacuolar change is seen in MF, which is often grouped with vacuolar interface dermatitis (Ramos-Ceballos and Horn 2010). A subset of MF patients with lichenoid reaction pattern is often associated with pruritus (Guitart et al. 1997). Extensive vacuolar change and spongiosis are unusual in MF and are more often seen in reactive vacuolar interface dermatitides such as drug eruptions, viral exanthems, graft versus host disease, connective tissue disorders, and pityriasis lichenoides. Vacuolar change and tagging of basal epidermis by atypical lymphocytes are seen in an example of hypopigmented MF; see Fig. 1.5.

In association with variable hypo- or hyperpigmented atrophic epidermis, with melanophages and/or band-like or perivascular

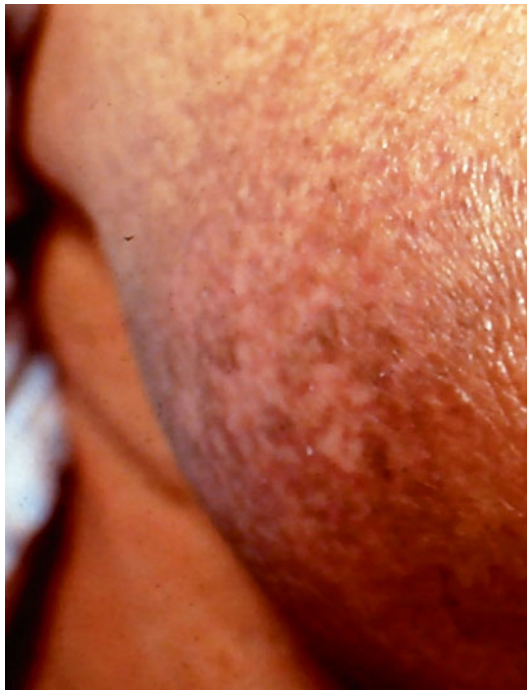

Fig. 1.9 Poikilodermatous MF on skin of breast

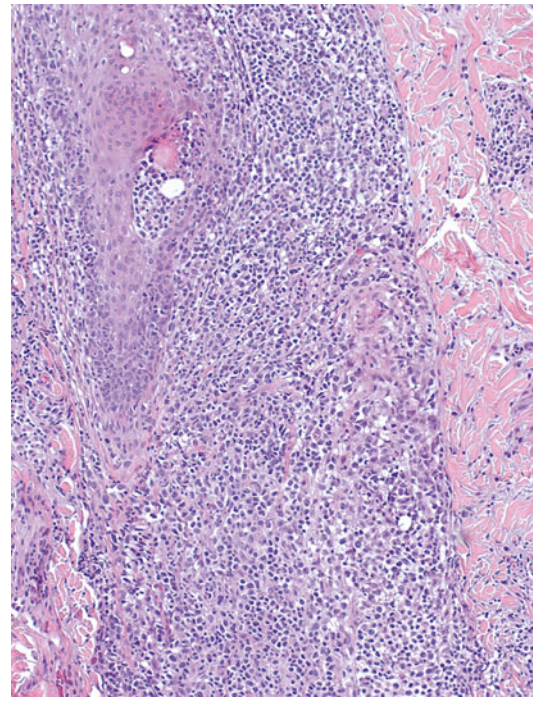

Fig. 1.10 Pseudolymphomatous folliculitis

lymphoid infiltrate, poikilodermatous lichenoid changes could be seen in a variety of sun-damaged dermatitis, rare childhood poikilodermatitis, and dermatomyositis as well as in regressive phases of classic MF or a subtype called poikilodermatous MF. This subtype, which has predilection to certain locations such as on the breasts, is indolent and has reduced risk for disease progression by multivariate analysis (Agar et al. 2010) (Fig. 1.9).

Histiocytes and inflammatory elements are also seen in lichenoid inflammatory infiltrates (Magro and Crowson 2000), but when extensive and appear as a lymphoid-rich sarcoid-like pattern, granulomatous MF should be considered. Clusters of histiocytes and foreign body giant cells are common features of cutaneous lymphoid hyperplasia or pseudolymphomas (Rijlaarsdam and Willemze 1993, 1994). Infections show histiocytic or acute inflammatory reactions. See Chap. 14 for cutaneous infections and tropical diseases.

Folliculotropic Pseudolymphomatous Folliculitis (PLF)

Pseudolymphomatous folliculitis is a common pattern with exclusive involvement of the hair follicles by a dense lymphoid infiltrate (Fig. 1.10). In those cases, PLF is a subset of lymphoid hyperplasia with characteristic clinical and pathologic features showing perifollicular clustering of T-cell-associated dendritic cells with activation of pilosebaceous units. PLF is a reactive group of patterns of varied etiologies, including lupus, rosacea, acne, and nonspecific bacterial infections, that have to be differentiated from malignant lymphomas and other cutaneous pseudolymphomas (Arai et al. 1999).

Hair follicles can be infiltrated by tumor cells in CTCL in a variant known as pilotropic or folliculotropic mycosis fungoides or follicular mucinosis-associated CTCL. Syringotropic and basaloid lymphomatous folliculitis is one of the five patterns seen in follicular MF (Gerami et al. 2008). Infiltration of hair follicles and sebaceous

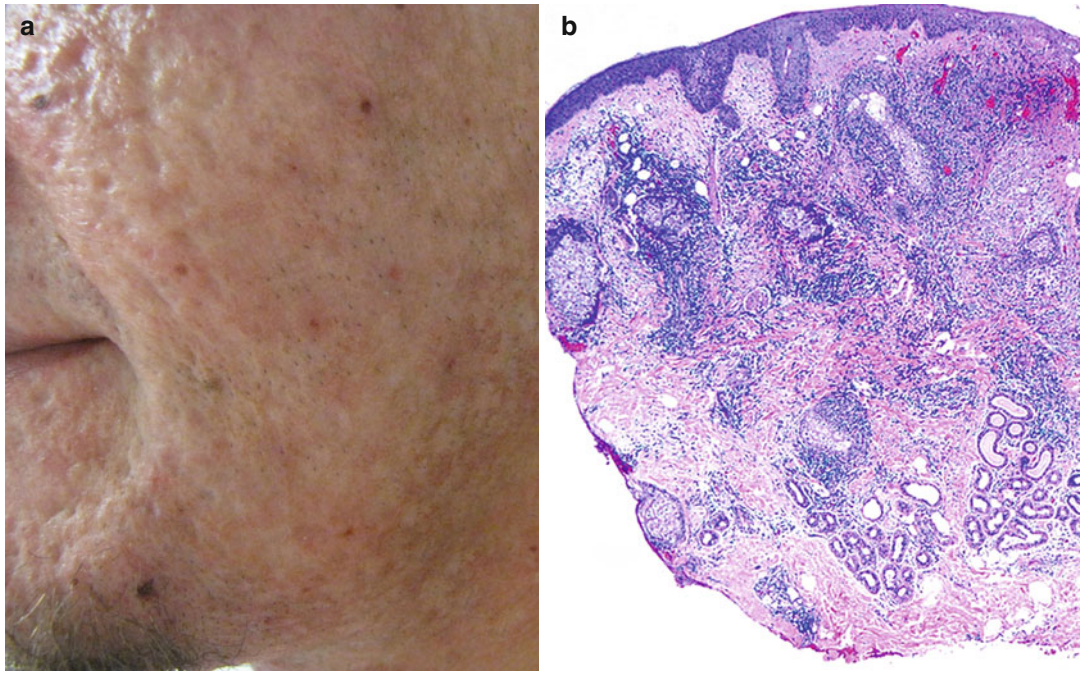

Fig. 1.11 (**a**) Head and neck folliculotropic MF in a young male. (**b**) Histopathology (Courtesy of Neil Fenske, Chair Dermatology and Frank Glass, Dermatopathologist, University of South Florida)

units can be accompanied by mucinous change in a phenomenon known as follicular mucinosis (Cerroni et al. 2002; Cerroni 2010; Cerroni and Kerl 2004). This event appears to forecast a poorer prognosis in MF; folliculotropic MF appears to be an aggressive variant of MF (Gerami et al. 2008; van Doorn et al. 2002). Folliculotropic MF without mucinosis is seen in about 50 %, epidermotropism along with folliculotropic MF in 25 %, and syringotropic involvement with folliculotropic MF in less than 10 % (Gerami et al. 2008) (Fig. 1.11).

Dermotropic

Nodules with Germinal Centers: Pseudolymphomatous B-Cell Pattern

This pattern is conventionally applied to a dense lymphoid infiltrate in the dermis or subcutaneous tissue showing discrete germinal centers (Burg et al. 2006) (Fig. 1.12). In studies that reviewed cutaneous lymphoid hyperplasia or cutaneous pseudolymphomas, Arai et al. detected up to 7 %

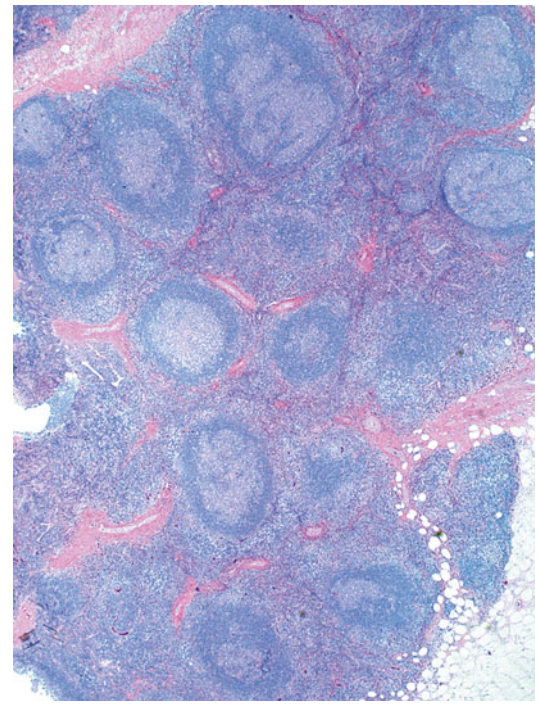

Fig. 1.12 Pseudolymphomatous pattern with several discrete follicles with germinal centers

with cutaneous lymphomas, typically of the cutaneous marginal zone type (Arai et al. 2005).

Nodules with Granulomas: Granulomatous Pattern

Granulomas are frequently seen in T- and B-cell pseudolymphomas. Granulomas consisting of aggregates of histiocyte/macrophages, without the necrosis, are also seen in infectious disease, e.g., tuberculosis, fungal infections, and others. Granulomas may be the prominent histopathology of a peculiar variant of mycosis fungoides known as granulomatous slack skin, or granulomatous MF, a mycosis fungoides variant without slack skin. According to a recent multicenter study of the Cutaneous Lymphoma Histopathology Task Force Group of the European Organization for Research and Treatment of Cancer (EORTC), granulomatous CTCLs show a therapy-resistant, slowly progressive course. The prognosis of GMF appears worse than that of classic non-granulomatous mycosis fungoides (Kempf et al. 2008). See Chap. 6 for discussion of granulomatous MF.

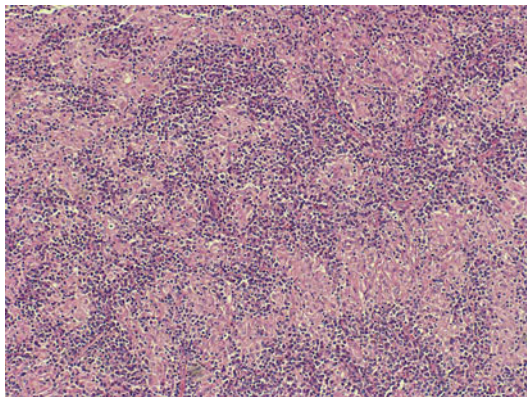

Fig. 1.13 Histiocytosis pattern seen in cutaneous Rosai-Dorfman. Also typical of Lennert's lymphohistiocytic pattern

A reactive granulomatous dermatitis is common in both T- and B-cell lymphomas. See Fig. 1.13 sarcoidosis involves the skin with spheroids of epithelioid granulomas with minimal lymphocytic component; see Chap. 13.

Histiocytosis Pattern. Reactive necrotizing histiocytic granulomatous dermatitis is the hallmark of Kikuchi-Fujimoto's disease involving the skin (Fig. 1.14). The presence of loose array of plump giant epithelioid histiocytes with cytophagocytosis or emperipolesis is seen in cutaneous Rosai-Dorfman disease (Fig. 1.15). See Chap. 13 for discussion of cutaneous histiocytic disorders.

Nodular T-Cell Cell Pattern: Nodules without germinal centers

Although this pattern is often associated with a B-cell pseudolymphomatous pattern, in our experience, the nodules of T cells is a common presentation of idiopathic nonclonal T-cell

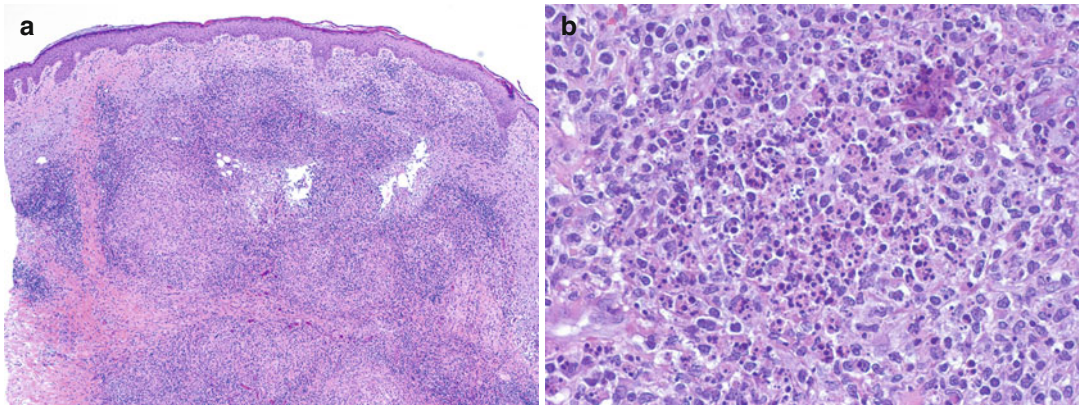

Fig. 1.14 Kikuchi's granulomatous dermatitis. (**a**) Low-power view with skin and underlying granulomatous necrotizing pattern. (**b**) Typical numerous apoptotic histiocytes with densely pyknotic nuclear debris and lack of neutrophils

pseudolymphoma and in many non-MF T-cell neoplasms (Fig. 1.16). See Chaps. 8 and 10.

Nodules with Increased Vessels

Capillary hemangiomas or granulation wound healing shows increased vessels with thin-walled endothelial lining cells. When "high," cuboidal or plump endothelial cells are seen, in concert with atypical small and medium pleomorphic T cells, cutaneous involvement of angioimmunoblastic T-cell lymphoma should be suspected, if the clinical presentation shows typical systemic wide features (Fig. 1.17). Prominent endothelial venules with plump pink cytoplasm, sometimes arborizing, surrounded by perivascular atypical small- and medium-sized pleomorphic lymphocytes that coexpress T cell and follicle center cell-associated markers, such as CD10, Bcl-6, and PD-1, suggest a cutaneous involvement by angioimmunoblastic T-cell lymphoma, a systemic disease with frequent skin involvement (Martel et al. 2000; Patsouris et al. 1989).

Medium-sized vessels are prominently involved in (angiocentric) NK/T-cell lymphomas, nasal type of extranodal or extranasal lymphomas. Vessel walls are often necrotic and occluded with resulting infarct and eschar formation in the skin. Angionecrotic, occluded vessels with cutaneous eschars have been described in a variant of lymphomatoid papulosis, type E (Kempf et al. 2013)

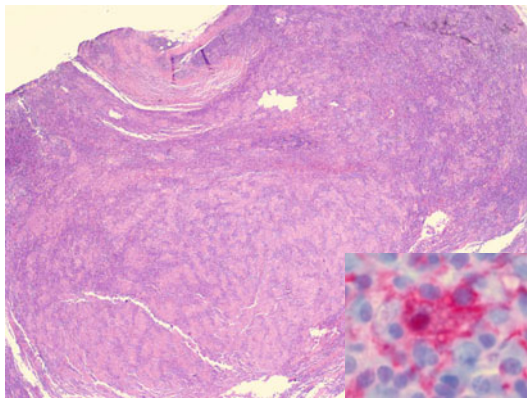

Fig. 1.15 Rosai-Dorfman in skin with *inset* of S100-positive histiocyte with emperipolesis of lymphocytes bounded by the irregular pinkish dendritic borders

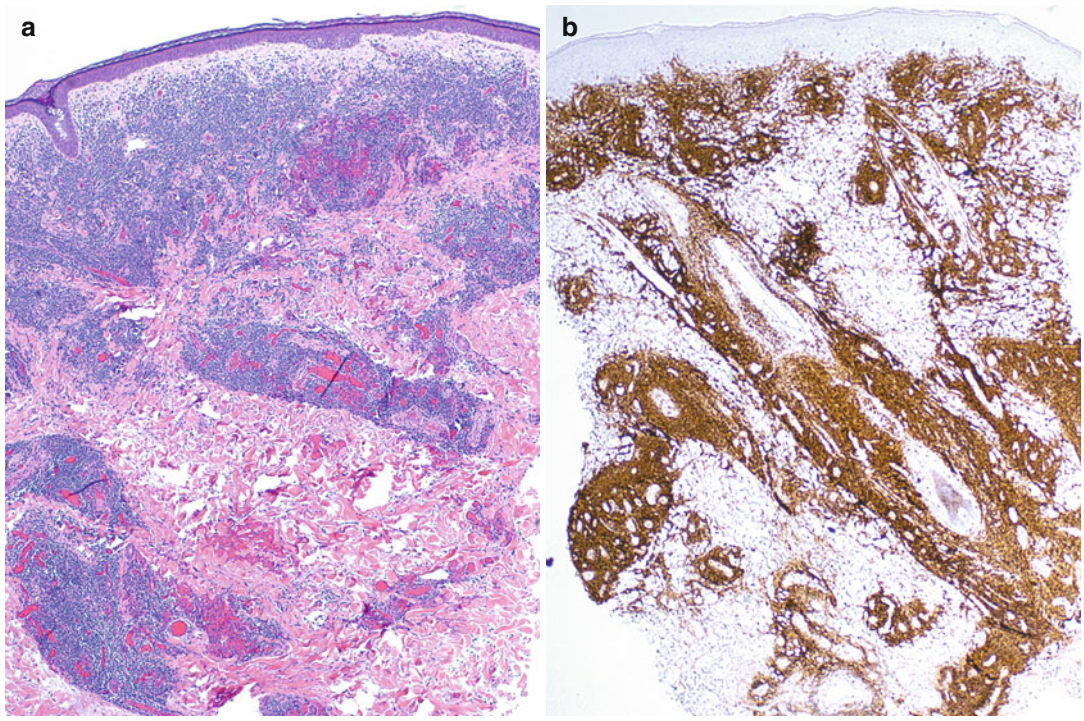

Fig. 1.16 (**a**) Nodular T-cell pseudolymphoma secondary to persistent reaction after a spider bite. (**b**) Low-power view of CD4-positive lymphocytes; T-cell receptor gene is germline

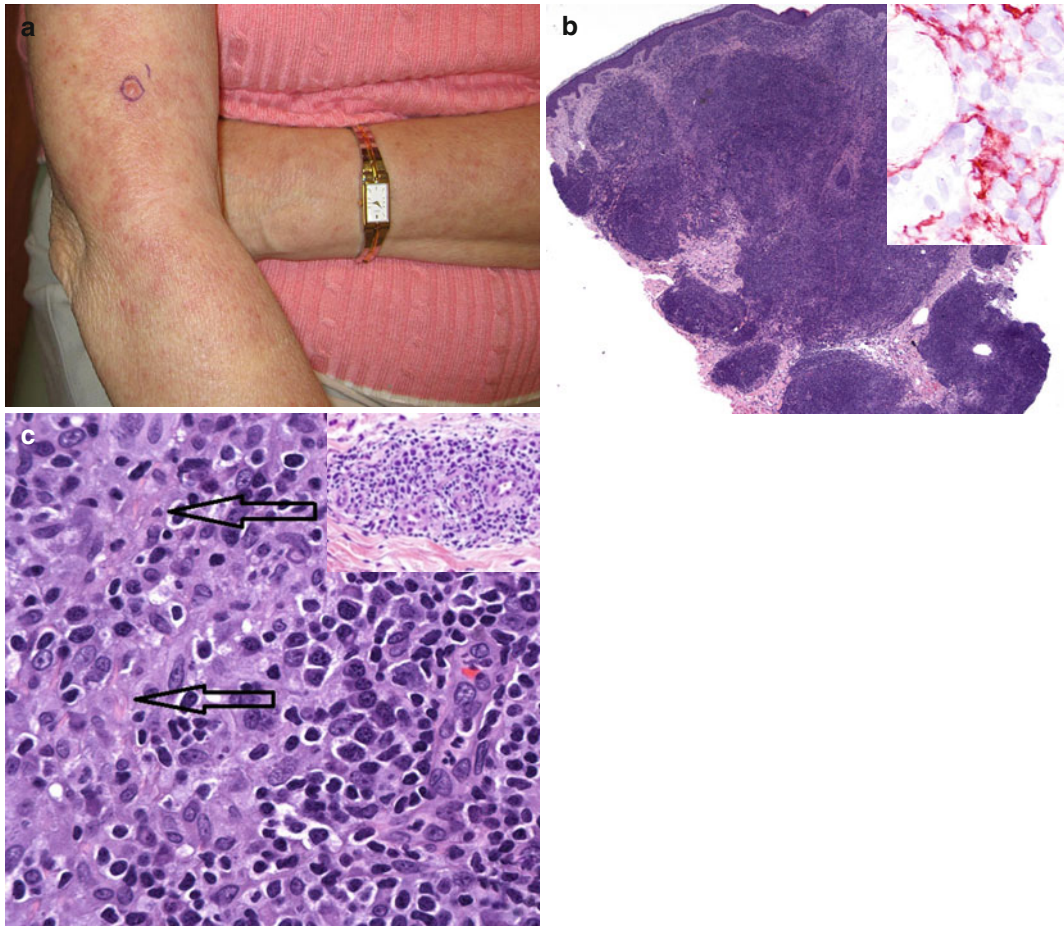

Fig. 1.17 (**a**) Clinic photo of erythematous rash with a nodule that was biopsied. (**b**) Nodular form of AITL with *inset* of CD10+ T cells. (**c**) High-power view with plasma cells and pink vessel deposits (*arrows*), *inset*. Subtle AITL histopathology with plump endothelial venules surrounded by atypical pleomorphic lymphocytes (Courtesy of Neil Fenske, Chair Dermatology and Frank Glass, University of South Florida)

(Fig. 1.18). Scant perivascular lymphoid infiltrates are a common manifestation of early MF or many reactive lymphoid infiltrates in a nonspecific reaction to autoimmune or drug-induced dermatitis.

Nodules with Increased Vessels and Eosinophils

Angiolymphoid hyperplasia with eosinophilia presents with concentrated eosinophils, some form of vascular malformation, and reactive lymphocytes (Fig. 1.19). Kimura's disease is a differential diagnosis, when no arteriovenous malformation is seen. Drug hypersensitivity reactions may show increased vessels and eosinophils. History is critical and previous therapy may disclose findings seen in cutaneous reactions to biological modifiers. See Chap. 15 for discussion of skin reactions secondary to biological modifiers and chemokine treatment.

Nodules with Increased Plasma Cells

Plasma cells at the edges of nodules of T cells are commonly seen in T-cell pseudolymphomas. When sheets of plasma cells are associated with expanded marginal zones and reactive germinal centers, cutaneous marginal zone lymphoma has to be considered (Fig. 1.20). Nodules of plasma cells that express high IgG4 subset are pathognomonic of

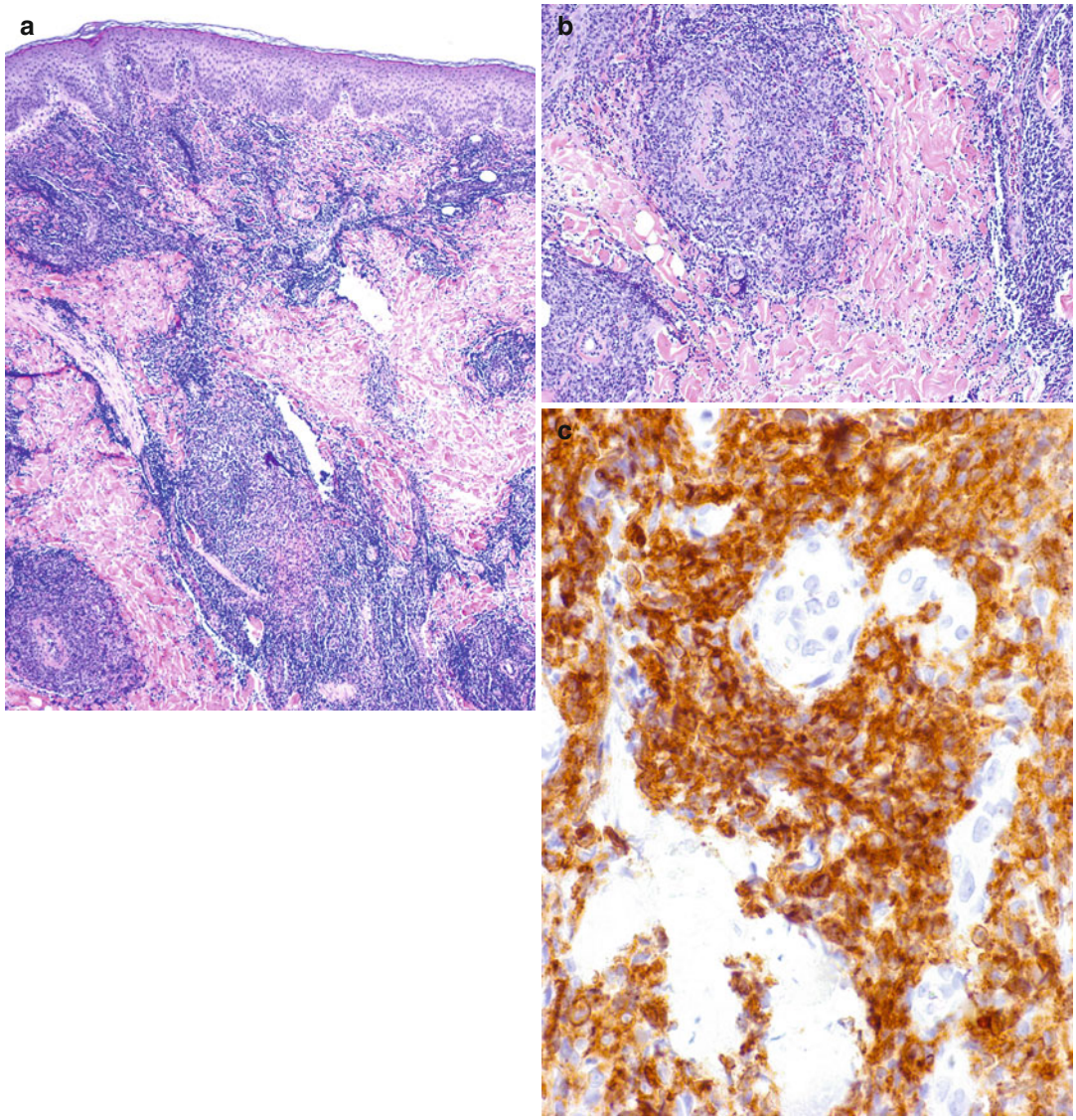

Fig. 1.18 (**a**) Lymphomatoid papulosis type E, low-power view. (**b**) Medium-power view of angiocentric pattern with occluded vessel. (**c**) CD30-positive infiltrate in LyP E subtype (Courtesy of Frank Glass, Aurora and USF Dermatopathology, Tampa, FL)

cutaneous manifestation of IgG4 disease (Cheuk and Chan 2010; Divatia et al. 2012).

Dermal Wedge-Shaped and Perivascular Pattern

This pattern is almost always described with lymphomatoid papulosis type A (Burg et al. 2006) but may not be present or clearly wedge shaped but nodular or perivascular in superficial biopsies or where the biopsy only shows part or half of the wedge or in other types of LyP. See Chap. 12 for discussion of these diseases.

Diffuse Pattern

Diffuse pattern is commonly associated with a nodular pattern, at least focally, and is seen in the dermis, subcutaneous tissue, or both. It can be seen in cases of T-cell pseudolymphomas

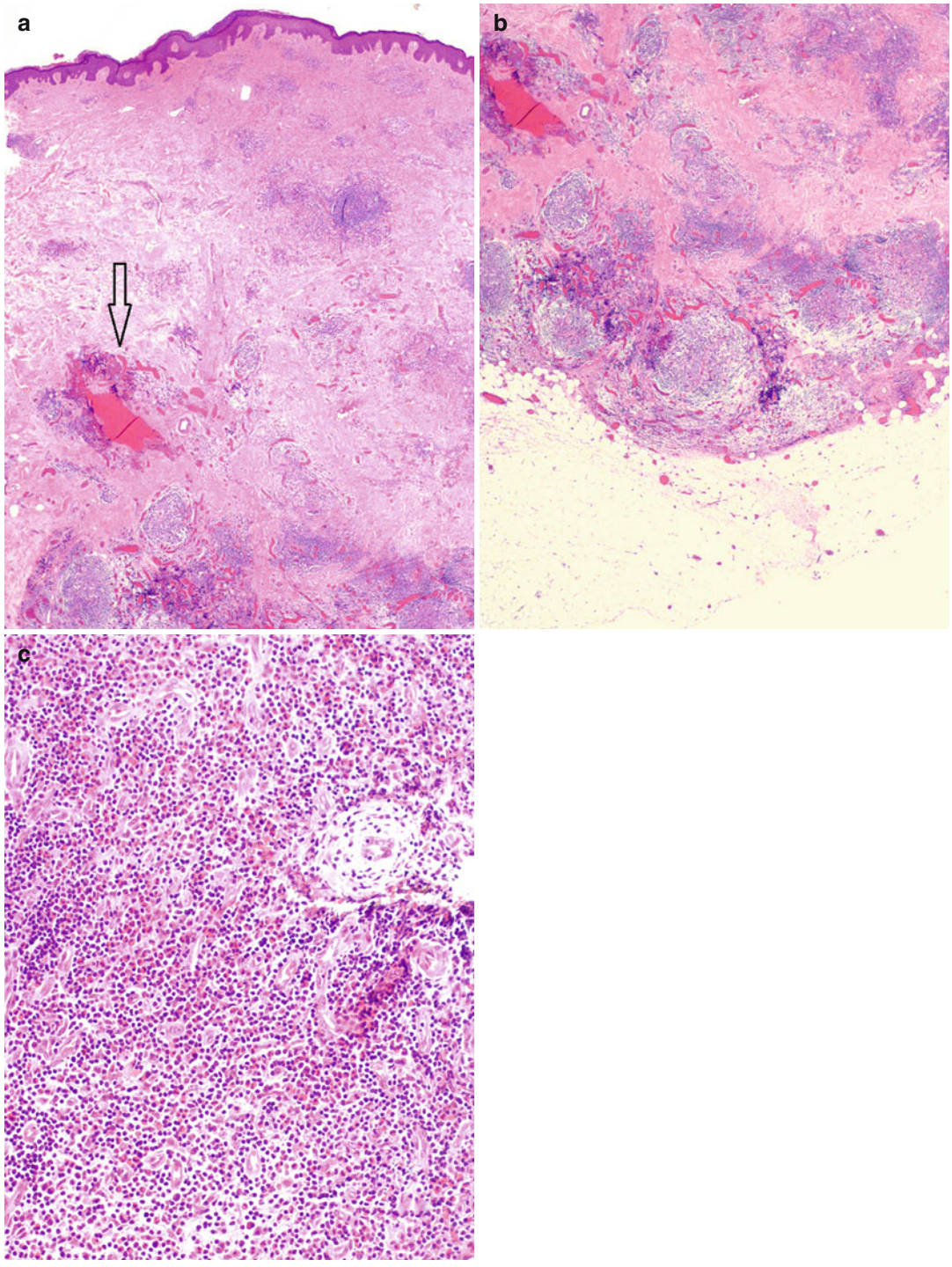

Fig. 1.19 (**a**) Angiolymphoid hyperplasia with eosinophilia showing vascular malformation (*arrow*), sclerosis, and lymphoid hyperplasia. (**b**) Medium-power view of arteriovenous malformation. (**c**) Vascular congestion, eosinophilia, and lymphoid infiltrate

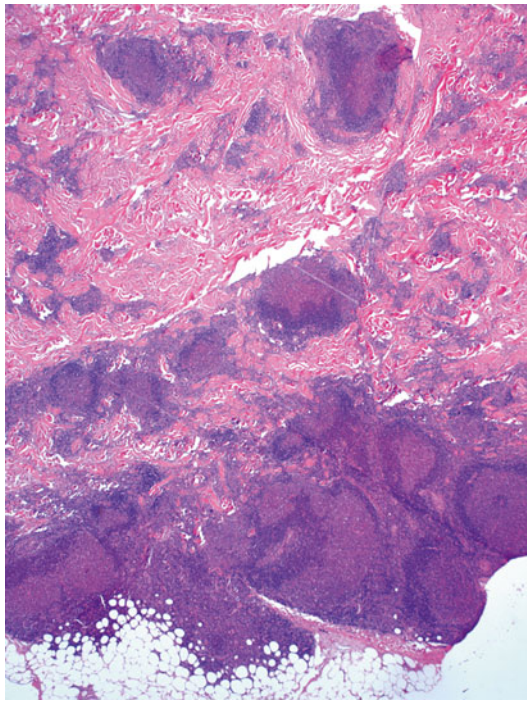

Fig. 1.20 Cutaneous marginal zone lymphoma with a nodular pattern showing paler germinal centers and diffuse interfollicular collection of lymphocytes arising from expansion of neoplastic marginal zones

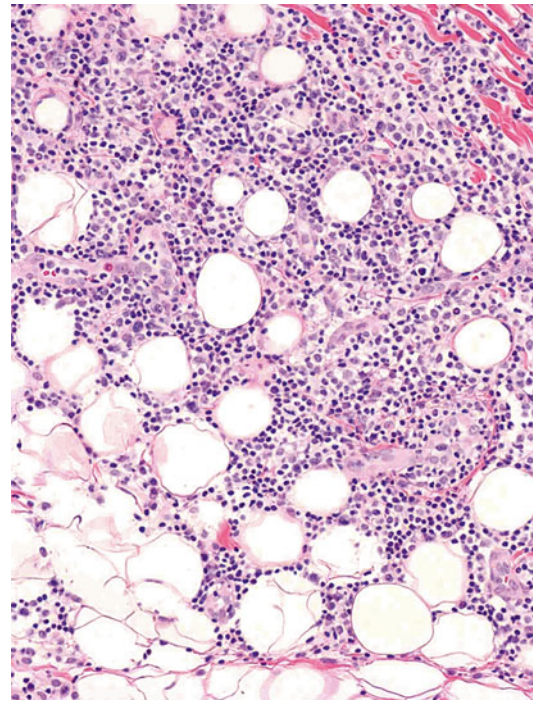

Fig. 1.21 Subcutaneous panniculitis in a patient with lupus profundus

secondary to drugs or to antigen-induced hypersensitivity reactions, and these cases are often associated with tissue eosinophils and plasma cells. When eosinophils or plasma cells are associated with a diffuse pattern with atypical small to medium or medium to large cells, with increased mitosis, lymphoma should be suspected.

Cytologic examination on high-power view will reveal whether the cells are predominantly of one or two types. In the diffuse large B-cell lymphoma, leg type, immunoblasts, or centroblasts predominate. In transformed MF, at least 25 % are large cells with small cerebriform cells in the background. If the large cells are less than 25 % and the lump is solitary or few, with lymphocytes composed of atypical small- and medium-sized population that are monoclonal by T-cell gene rearrangement, then a primary cutaneous small- and medium-sized T-cell lymphoma is a prime consideration (see Chap. 10 for discussion of these entities).

Subcutaneous Pattern

Subcutaneous pattern is seen in both reactive and neoplastic processes. A predominantly septal panniculitis is typical of erythema nodosum, often bilateral on extensor surfaces of the lower extremities, and secondary to varied etiology; foremost are infections, i.e., mycobacteria or leprosy.

Predominantly nodular panniculitis is typical of lupus profundus, cytophagic histiocytic panniculitis, atypical lobular lymphocytic panniculitis, and subcutaneous panniculitic T-cell lymphoma (see Chap. 11 for discussion of subcutaneous pattern) (Fig. 1.21).

Miscellaneous Patterns

Intravascular Pattern

This is a rare pattern which occasionally baffles the pathologist because of the peculiar localization of the atypical cells within dermal blood vessels.

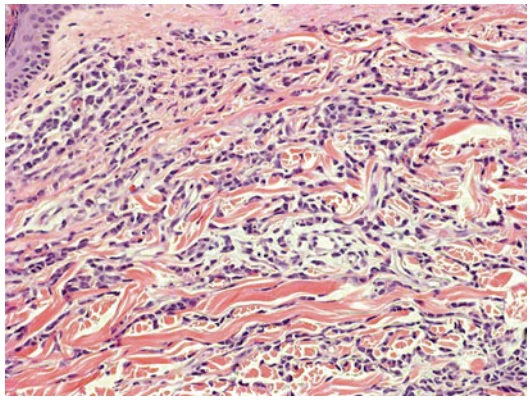

Fig. 1.22 Single-file pattern in hematodermic or blastic plasmacytoid dendritic cell neoplasm. Note the plasmacytoid violaceous appearance of the blasts

This pattern upon further immunohistologic stains would be seen in a variety of lymphomas including intravascular large B- and T-cell lymphomas, intravascular histiocytosis, and/or even the rare recently described cases simulating intravascular CD30+ lymphomas. Intravascular involvement of lymphomas is readily detected in skin biopsies. Please see Chap. 17 for discussion of intravascular lymphomas.

Single-File Pattern

Single-file pattern could be seen in myelomonocytic and lymphoid leukemias involving the skin. Please see Chap. 16 for discussion of leukemic, histiocytic, and myelomonocytic skin pattern. Caution has to be exercised in interpreting a low-grade lymphoma insinuating small non-blastic lymphoid cells between collagen fibers as a single-file pattern. Often the single-file pattern in leukemia is seen next to the epidermis in a horizontal array, without sclerosis, and admixed with a targetoid or diffuse pattern deeper in the dermal and subcutaneous tissue (Fig. 1.22).

References

Agar NS, Wedgeworth E, Crichton S, Mitchell TJ, Cox M, Ferreira S, Robson A, Calonje E, Stefanato CM, Wain EM, Wilkins B, Fields PA, Dean A, Webb K, Scarisbrick J, Morris S, Whittaker SJ. Survival outcomes and prognostic factors in mycosis fungoides/Sezary syndrome: validation of the revised International Society for Cutaneous Lymphomas/European Organisation for Research and Treatment of Cancer staging proposal. J Clin Oncol. 2010;28(31):4730–9.

Arai E, Okubo H, Tsuchida T, Kitamura K, Katayama I. Pseudolymphomatous folliculitis: a clinicopathologic study of 15 cases of cutaneous pseudolymphoma with follicular invasion. Am J Surg Pathol. 1999;23(11):1313–9.

Arai E, Shimizu M, Hirose T. A review of 55 cases of cutaneous lymphoid hyperplasia: reassessment of the histopathologic findings leading to reclassification of 4 lesions as cutaneous marginal zone lymphoma and 19 as pseudolymphomatous folliculitis. Hum Pathol. 2005;36(5):505–11.

Baldassano MF, Bailey EM, Ferry JA, Harris NL, Duncan LM. Cutaneous lymphoid hyperplasia and cutaneous marginal zone lymphoma: comparison of morphologic and immunophenotypic features. Am J Surg Pathol. 1999;23(1):88–96.

Bergman R. Pseudolymphoma and cutaneous lymphoma: facts and controversies. Clin Dermatol. 2010;28(5):568–74.

Bergman R, Khamaysi K, Khamaysi Z, Ben AY. A study of histologic and immunophenotypical staining patterns in cutaneous lymphoid hyperplasia. J Am Acad Dermatol. 2011;65(1):112–24.

Bocquet H, Bagot M, Roujeau JC. Drug-induced pseudolymphoma and drug hypersensitivity syndrome (Drug Rash with Eosinophilia and Systemic Symptoms: DRESS). Semin Cutan Med Surg. 1996;15(4):250–7.

Bradford PT, Devesa SS, Anderson WF, Toro JR. Cutaneous lymphoma incidence patterns in the United States: a population-based study of 3884 cases. Blood. 2009;113(21):5064–73.

Burg G, Kempf W, Cozzio A, Dobbeling U, Feit J, Golling P, Michaelis S, Scharer L, Nestle F, Dummer R. Cutaneous malignant lymphomas: update 2006. J Dtsch Dermatol Ges. 2006;4(11):914–33.

Caro WA. Biopsy in suspected malignant lymphoma of the skin. Cutis. 1978;21(2):197–201.

Caro WA, Helwig HB. Cutaneous lymphoid hyperplasia. Cancer. 1969;24(3):487–502.

Ceballos KM, Gascoyne RD, Martinka M, Trotter MJ. Heavy multinodular cutaneous lymphoid infiltrates: clinicopathologic features and B-cell clonality. J Cutan Pathol. 2002;29(3):159–67.

Cerroni L. Lymphoproliferative lesions of the skin. J Clin Pathol. 2006;59(8):813–26.

Cerroni L. Pilotropic mycosis fungoides: a clinicopathologic variant of mycosis fungoides yet to be completely understood. Arch Dermatol. 2010;146(6):662–4.

Cerroni L, Kerl H. Primary follicular mucinosis and association with mycosis fungoides and other cutaneous T-cell lymphomas. J Am Acad Dermatol. 2004;51(1):146–7.

Cerroni L, Fink-Puches R, Back B, Kerl H. Follicular mucinosis: a critical reappraisal of clinicopathologic features and association with mycosis fungoides and Sezary syndrome. Arch Dermatol. 2002;138(2):182–9.

Cerroni L, Gatter K, Kerl H. Skin lymphoma: the illustrated guide, Wiley-Blackwell, Hoboken, NJ, USA; 3rd. 2009.

Cheuk W, Chan JK. IgG4-related sclerosing disease: a critical appraisal of an evolving clinicopathologic entity. Adv Anat Pathol. 2010;17(5):303–32.

Colli C, Leinweber B, Mullegger R, Chott A, Kerl H, Cerroni L. Borrelia burgdorferi-associated lymphocytoma cutis: clinicopathologic, immunophenotypic, and molecular study of 106 cases. J Cutan Pathol. 2004;31(3):232–40.

Criscione VD, Weinstock MA. Incidence of cutaneous T-cell lymphoma in the United States, 1973–2002. Arch Dermatol. 2007;143(7):854–9.

Divatia M, Kim SA, Ro JY. IgG4-related sclerosing disease, an emerging entity: a review of a multi-system disease. Yonsei Med J. 2012;53(1):15–34.

Furudate S, Fujimura T, Kambayashi Y, Aiba S. Profiles of cytotoxic T lymphocytes in cutaneous lymphoid hyperplasia of the face. Case Rep Dermatol. 2013;5(1):88–92.

Gerami P, Rosen S, Kuzel T, Boone SL, Guitart J. Folliculotropic mycosis fungoides: an aggressive variant of cutaneous T-cell lymphoma. Arch Dermatol. 2008;144(6):738–46.

Guitart J, Deonision J, Kadin M. CD30 lymphoproliferative disorders with pseudoepitheliomatous hyperplasia: a possible role for Th17 cytokines, neutrophils and eosinophils. 2nd world congress on cutaneous lymphomas, Berlin; 2013. Abstract 48.

Guitart J, Peduto M, Caro WA, Roenigk HH. Lichenoid changes in mycosis fungoides. J Am Acad Dermatol. 1997;36(3 Pt 1):417–22.

Isaacson PG, Norton AJ. Cutaneous lymphomas. In: Extranodal lymphomas. Edinburgh: Churchill Livingstone; 1994. p. 131–91.

Jenni D, Karpova MB, Seifert B, Golling P, Cozzio A, Kempf W, French LE, Dummer R. Primary cutaneous lymphoma: two-decade comparison in a population of 263 cases from a Swiss tertiary referral centre. Br J Dermatol. 2011;164(5):1071–7.

Kempf W, Kazakov D, Scharer L, et al. Angioinvasive lymphomatoid papulosis: a new variant simulating aggressive lymphomas. Am J Surg Pathol. 2013; 37:1–3.

Kempf W, Ostheeren-Michaelis S, Paulli M, Lucioni M, Wechsler J, Audring H, Assaf C, Rudiger T, Willemze R, Meijer CJ, Berti E, Cerroni L, Santucci M, Hallermann C, Berneburg M, Chimenti S, Robson A, Marschalko M, Kazakov DV, Petrella T, Fraitag S, Carlotti A, Courville P, Laeng H, Knobler R, Golling P, Dummer R, Burg G. Granulomatous mycosis fungoides and granulomatous slack skin: a multicenter study of the Cutaneous Lymphoma Histopathology Task Force Group of the European Organization For Research and Treatment of Cancer (EORTC). Arch Dermatol. 2008;144(12):1609–17.

Kojima M, Nakamura N, Sakamoto K, Sakurai S, Tsukamoto N, Itoh H, Ikota H, Enomoto Y, Shimizu K, Motoori T, Hoshi K, Igarashi T, Masawa N, Nakamine H. Progressive transformation of the germinal center of extranodal organs: a clinicopathological, immunohistochemical, and genotypic study of 14 cases. Pathol Res Pract. 2010a;206(4):235–40.

Kojima M, Sakurai S, Shimizu K, Itoh H. B-cell cutaneous lymphoid hyperplasia representing progressive transformation of germinal center: a report of 2 cases. Int J Surg Pathol. 2010b;18(5):429–32.

Lai P, Hsiao Y, Hsu J, Wey SJ. Early stage mycosis fungoides with focal CD30-positive large cell transformation. Dermatol Sin. 2012;31(2):1–5. doi:http://dx.doi.org/10.1016/j.dsi.2012.06.006.

Lipsker D. Dermatological aspects of Lyme borreliosis. Med Mal Infect. 2007;37(7–8):540–7.

Magro CM, Crowson AN. Drug-induced immune dysregulation as a cause of atypical cutaneous lymphoid infiltrates: a hypothesis. Hum Pathol. 1996;27(2):125–32.

Magro CM, Crowson AN. Lichenoid and granulomatous dermatitis. Int J Dermatol. 2000;39(2):126–33.

Magro CM, Crowson AN, Harrist TJ. Atypical lymphoid infiltrates arising in cutaneous lesions of connective tissue disease. Am J Dermatopathol. 1997;19(5):446–55.

Magro CM, Crowson AN, Kovatich AJ, Burns F. Drug-induced reversible lymphoid dyscrasia: a clonal lymphomatoid dermatitis of memory and activated T cells. Hum Pathol. 2003;34(2):119–29.

Martel P, Laroche L, Courville P, Larroche C, Wechsler J, Lenormand B, Delfau MH, Bodemer C, Bagot M, Joly P. Cutaneous involvement in patients with angioimmunoblastic lymphadenopathy with dysproteinemia: a clinical, immunohistological, and molecular analysis. Arch Dermatol. 2000;136(7):881–6.

Muramoto L, Kadin M. Improved detection of lymphoid cell surface antigens in tissues fixed in periodate-lysine-paraformaldehyde. Am J Clin Pathol. 1987;88:589–95.

Oliver GF, Winkelmann RK, Muller SA. Lichenoid dermatitis: a clinicopathologic and immunopathologic review of sixty-two cases. J Am Acad Dermatol. 1989;21(2 Pt 1):284–92.

Patsouris E, Noel H, Lennert K. Angioimmunoblastic lymphadenopathy–type of T-cell lymphoma with a high content of epithelioid cells. Histopathology and comparison with lymphoepithelioid cell lymphoma. Am J Surg Pathol. 1989;13(4):262–75.

Ramos-Ceballos F, Horn TD. Interface dermatitis. In: Barnhill RL, Crowson AN, Magro CM, et al., editors. Dermatopathology. 3rd ed. China: McGraw Hill Medical; 2010. pp. 342–344.

Rijlaarsdam JU, Willemze R. Diagnosis and classification of cutaneous pseudolymphoma. Historical review and perspectives. Ann Dermatol Venereol. 1993;120(1): 100–6.

Rijlaarsdam JU, Willemze R. Cutaneous pseudolymphomas: classification and differential diagnosis. Semin Dermatol. 1994;13(3):187–96.

Singh ZN, Tretiakova MS, Shea CR, Petronic-Rosic VM. Decreased CD117 expression in hypopigmented mycosis fungoides correlates with hypomelanosis: lessons learned from vitiligo. Mod Pathol. 2006;19(9):1255–60.

Swerdlow SJ, Campo E, Harris NL, Jaffe ES, Pileri S, Stein H, Thiele J, Vardiman JW, editors. WHO classification of tumors of haematopoieitic and lymphoid tissues, WHO press, Geneva, Switzerland; 4th ed. 2008.

van Doorn R, Scheffer E, Willemze R. Follicular mycosis fungoides, a distinct disease entity with or without associated follicular mucinosis: a clinicopathologic and follow-up study of 51 patients. Arch Dermatol. 2002;138(2):191–8.

Vonderheid EC, Pavlov I, Delgado JC, Martins TB, Telang GH, Hess AD, Kadin M, et al. Prognostic factors and risk stratification in early mycosis fungoides. Leuk Lymphoma. 2014;55(1):44–50. doi: 10.3109/10428194.2013.790541. Epub 2013 May 7.

Willemze R, Jaffe ES, Burg G, Cerroni L, Berti E, Swerdlow SH, Ralfkiaer E, Chimenti S, az-Perez JL, Duncan LM, Grange F, Harris NL, Kempf W, Kerl H, Kurrer M, Knobler R, Pimpinelli N, Sander C, Santucci M, Sterry W, Vermeer MH, Wechsler J, Whittaker S, Meijer CJ. WHO-EORTC classification for cutaneous lymphomas. Blood. 2005;105(10):3768–85.