
Functional Organization of the Skin as an Immune Response Organ: Skin, Immune Response, and Useful Immunohistochemistry

2

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Introduction to Cutaneous Lymphoid Tissue

Skin Meets Environment

The skin is the body's major interface with the environment where it is exposed to a diverse repertoire of foreign antigens. It is also a highly susceptible portal of entry for infectious organisms. For its protective role, the skin has therefore developed highly effective immediate and long-term immune responses. The patterns of inflammatory responses may set the stage for the development of subsequent malignant lymphomas. Accordingly, malignant lymphocytes that traffic to and through the skin share many immunologic and genotypic features of their benign counterparts involved in cutaneous immune surveillance.

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Innate Immune Response

The innate immune system, also known as non-specific immune system and first line of defense, comprises the cells and mechanisms that defend the host from infection by other organisms in a nonspecific manner. This “innate” response is focused on early (minutes to hours) response to pathogens. Triggers of the innate immune response include microbial and foreign glycolipids, glycoproteins, and DNA complexes (Beetz et al. 2008; Holtmeier and Kabelitz 2005; Kabelitz 2011; Kabelitz et al. 2000). Cellular components of the innate immune system include neutrophils, mast cells, macrophages, dendritic cells, and effector lymphocytes. The immediate effector lymphocytes include natural killer (NK) cells and gamma-delta T cells (γ/δ T cells) (Kabelitz 1992; Kabelitz et al. 2005; Kim et al. 2005). The γ/δ T cells, which comprise 10 % of skin T lymphocytes, along with B cells and NK cells, are largely localized in the dermis and subcutaneous tissue and, for their role as immune effector cells, are also predisposed to the basal layer of the epidermis and outer root sheaths of hair follicles (Kabelitz 2011; Kabelitz et al. 2000).

Secondary Immune Response

The secondary immune responses require the regulation of circulating and peripheral memory T cells, and the skin is postulated to be an active

peripheral lymphoid organ, hosting 20 billion T cells, twice that in circulation (Egawa and Kabashima 2011). The adaptive or long-term component of the immune response is composed mainly of T cells bearing α/β T-cell antigen receptors (alpha-beta T cells). These so-called α/β T cells, which comprise 90 % of the cutaneous T cells, acquire homing capacity to the epidermis through the activation of surface addressins enabling them to interact with epidermal Langerhans cells for microbial recognition. Differential expression of surface receptors appears to determine T-cell localization. More than 90 % of these cells express cutaneous lymphocyte antigen (CLA), CD45RO and CCR4 receptors, which are characteristic surface antigens of effector memory T cells (Fig. 2.1). Unlike memory T cells common in the blood circulation and in lymph nodes (which additionally express CCR7 chemokine receptor), memory T cells resident in the skin lack the central memory T-cell marker CCR7 (Egawa and Kabashima 2011). The circulating central memory T-cell pool transiently expresses lymph node homing CCR7 and CD62L (L-selectin). Upon encountering its cognate antigens within the lymph nodes, these central memory T cells downregulate these markers and upregulate CLA + and other skin-specific homing addressins necessary for homing to the skin.

Cutaneous Trafficking of Lymphocytes

A subset of T lymphocytes migrate to the skin via dermal postcapillary venules and recirculate to regional lymph nodes that drain the skin, creating a local network of immune surveillance. For a detailed pictorial review, see (Clark 2010), (Fig. 2.1). This decades-old hypothesis by Streilein (Streilein 1978, 1983, 1985, 1989; Streilein and Bergstresser 1984) is supported by in vivo and in vitro observations and is validated in live mammalian studies by two-photon microscopy which visualize this regional network and

its dynamic stepwise development (Egawa et al. 2011). In addition, live animal skin color changes and microscopy of skin-associated lymphocytes trafficking from the lymph nodes is visualized using a technique relying on new fluorescent-tagged cells (Tomura 2012) which changes from fluorescent green to red upon exposure to skin-directed UV (ultraviolet) light (Kaplan et al. 2005, 2008). Accumulating evidence indicates that skin is a crucial modulator of the global immune response and is considered to be a crucial peripheral lymphoid organ akin to the lymph nodes (Egawa and Kabashima 2011).

An orchestrated set of ligand-receptor and chemokine exchanges between immune effector cells, epithelia, and dermal high endothelial venules lead to cutaneous lymphoid infiltrates. These lymphoid infiltrates generate a pattern of reaction that may appear more or less concentrated within the epidermis, dermis, and/or subcutaneous tissue depending on the main participating cells and the signals they receive. Remarkable inroads into the origin and function of the normal components of the immune response provide insights into the histologic architecture, phenotype, and behavior of malignant lymphoma/leukemia counterparts.

Cytokines Define Functional T Helper Subsets

Cytokines are the soluble hormonelike messengers active in mediating the immune response. Deregulation or overproduction of select cytokines is known to play a major role in the pathogenesis of common cutaneous inflammatory diseases, e.g., psoriasis (Schaerli et al. 2004; Wolk et al. 2009) and atopic dermatitis (Asarch et al. 2008; Koga et al. 2008). Ongoing research indicates that cytokines also are involved in the pathogenesis of cutaneous lymphomas (Saed et al. 1994; Vowels et al. 1994a, b). Clinical trials targeting cytokines and their receptors have shown promise for the treatment of cutaneous inflammatory and autoimmune diseases (Asarch et al. 2008; Miossec et al. 2009).

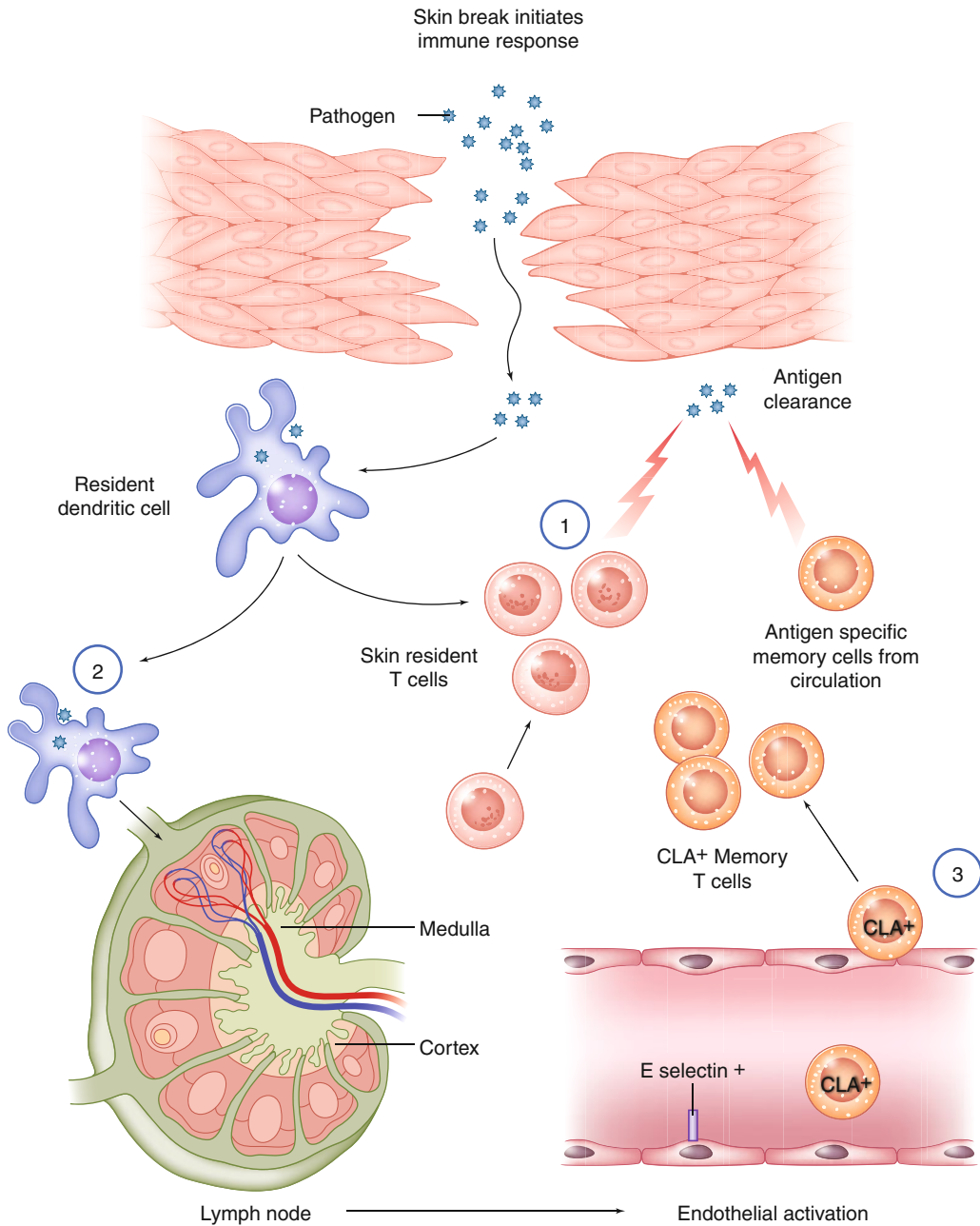


Fig. 2.1 The role of effector T cells and memory T cells in recall immune responses (Modified from Clark 2010). Memory immune responses can be divided into three stages. First, dendritic cells (DC) take up antigen following pathogen reexposure and present it to effector T resident locally within the skin. These cells proliferate and effect clearance of the pathogen. Second, DC carry endo-

cytosed antigen to the skin-draining lymph nodes where it is presented to central memory T cells. These cells then give rise to new populations of skin homing T effector cells that migrate to the skin and clear the infection; third, inflammation leads to endothelial activation and nonspecific recruitment of T cells from the blood

The interaction between proinflammatory T cells and regulatory T cells also determines cutaneous manifestations of graft-versus-host disease (Beres and Drobyski 2013). Serum cytokine/receptor levels are useful markers of disease activity and quantification of tumor burden (Wasik et al. 1996; Kadin et al. 2012). Therefore, we feel it is essential for our readers to have a basic understanding of cytokines and the cells that produce them.

Of the two main subsets of T lymphocytes, CD4 and CD8, the CD4 T helper subset (Th) is the main cytokine producer. Initially two main Th subset groups were defined by the cytokines they secrete. Th1 cells, regulated by transcription factors Tbet and STAT4, secrete IFN-gamma and induce inflammatory responses to intracellular pathogens. Th2 cells, regulated by GATA3 and STAT5, are represented by interleukins 4, 5, and 13, respond to extracellular parasites, and are associated with the promotion of IgE and eosinophilia. Th9 cells are closely related to Th2 cells but have the capacity to produce IL-9 and IL-10. IL-9 is produced by tumor cells in some anaplastic large cell lymphomas and Hodgkin lymphomas (Merz et al. 1991). More recently described Th17 cells, which recruit neutrophils and macrophages to sites of inflammation, are regulated by ROR and STAT3, convey autoimmune responses, and promote antimicrobial immunity at the body's borders, e.g., linings of the respiratory and gastrointestinal tracts and the skin. Th17 cells also can produce interleukin 22 which induces epithelial and mucosal cells to secrete antimicrobial peptides active against fungi and bacteria. The proinflammatory and autoimmune effects of Th17 cells are counterbalanced by natural and induced regulatory T cells (Tregs), regulated by the transcription factor FoxP3 and the secretion of immunosuppressive cytokines TGF-beta and IL-10. T cells associated with follicular center differentiation employ transcription factor Bcl-6 and appear to be the source of neoplastic cells in some primary cutaneous CD4+ small-/medium-sized pleomorphic T-cell lymphomas (Rodriguez Pinilla et al. 2009) and mycosis fungoides/Sezary syndrome cases (Meyerson et al. 2013).

CD4+ T cells demonstrate remarkable plasticity (Zhou et al. 2009). It appears that expression of Foxp3 by induced Treg cells (iTregs) or IL-17 by Th17 cells may not be stable. TGF-beta promotes Th17 cell differentiation in a concentration-dependent manner. At low concentrations, TGF-beta synergizes with interleukin IL-6 and IL-21 to promote IL-23 receptor (IL23R) expression, favoring Th17 cell differentiation. High concentrations of TGF-beta repress IL23R expression and favor the development of Foxp3+ Treg cells (Zhou et al. 2008). See Fig. 2.2 on the Th subset cytokines and transcription factors.

Duhen characterized a population of human skin-homing memory CD4+ T cells that express the chemokine receptors CCR10, CCR6, and CCR4 and produce IL-22 but neither IL-17 nor IFN-gamma. The differentiation of T cells producing only IL-22 is efficiently induced in naive T cells by plasmacytoid dendritic cells in an IL-6- and tumor necrosis factor-dependent manner (Duhen et al. 2009). Notch signaling drives IL-22 secretion in CD4+ T cells by stimulating the aryl hydrocarbon receptor (Alam et al. 2010).

An overview of Th subsets and the cytokines they produce is presented in Fig. 2.2 (and Table 2.1). For more detailed descriptions, readers are referred to several review articles (Maddur et al. 2012; Miossec et al. 2009; Zhou et al. 2009).

Functional Compartments

Epidermis: Generation of Lichenoid Infiltrate

Following antigen stimulation or injury to the skin, there is epidermal keratinocyte activation with lymphokine release. In addition, Toll-like receptors of dendritic antigen-presenting cells (APC) located in the epidermis and dermis are activated with antigenic epitopes from microbes or foreign bodies. Following antigen activation, Langerhans cells and plasmacytoid dendritic cells migrate to the lymph nodes draining the skin to recruit more lymphocytes.

Fig. 2.2 Overview of Th cell differentiation from naive CD4+ T cells. This diagram depicts the cytokines and transcription factors which determine naive CD4 T cell fates, the cytokines they produce, and their main effects

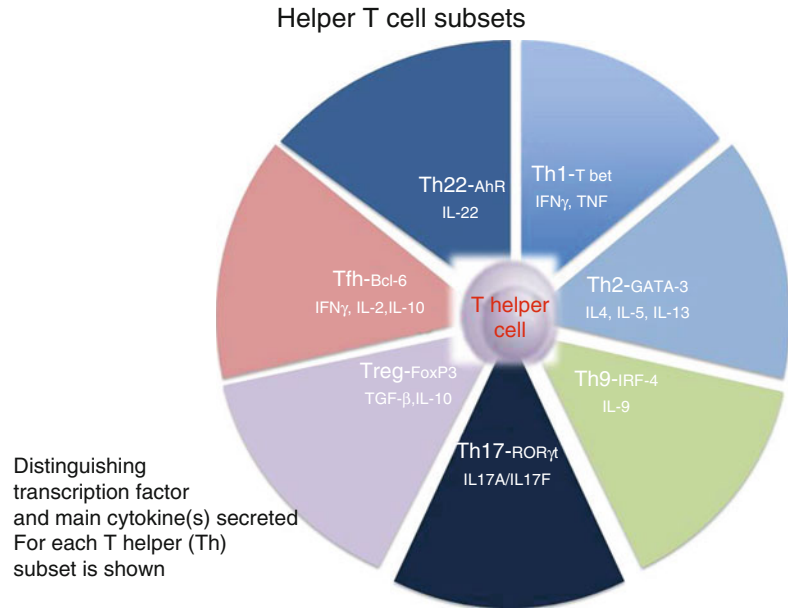
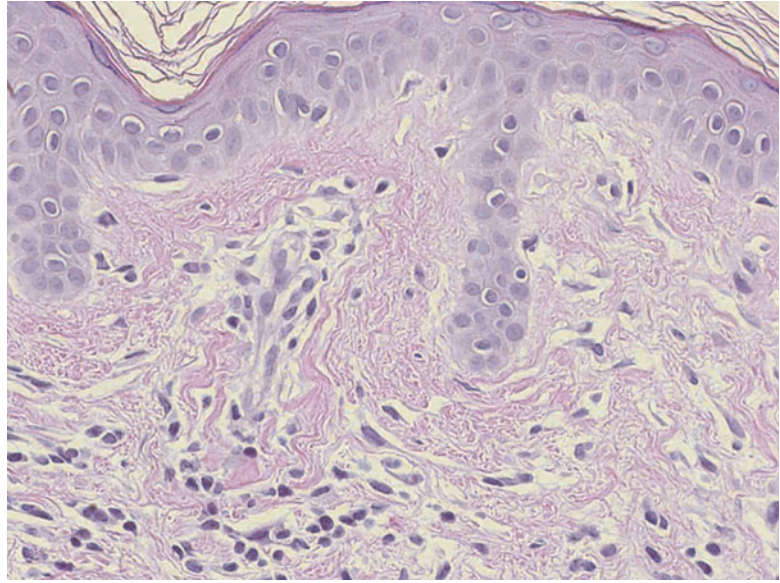


Table 2.1 T helper cell subsets

Th subset	Th1	Th2	Th17	Th9	Th22	Treg	Tfh
Transcription factors	Tbet, Stat4	GATA-3 Stat-5	ROR γ τ / RORC Stat3	IRF-4 PU.1	AhR Stat3	FoxP3 Stat5	Bcl-6 Stat3
Secreted cytokines	IFN γ , IL2 IL-10	IL-4, IL-5, IL-10, IL-13	IL-17A, IL-17F, IL21, IL-22	IL-9, IL-10	IL-22, IL-21, IL10, IL-13	TGF- β , IL-10	IFN γ , IL2, IL-4, IL-10, IL-17A, IL-17F
Main functions	Delayed hypersensitivity, macrophage activation, cytotoxic T-cell proliferation, nitric oxide production. Promote skin inflammatory disorders and autoimmunity	Humoral immunity, eosinophil activation Response to large extracellular pathogens	Response to fungi, extracellular bacteria Recruitment of neutrophils and macrophages, promote acute inflammation and autoimmunity	Defense against helminth infections, chronic allergic reaction	Synergize with Th17 cells to promote innate immunity in the skin and GI and respiratory tracts, promote tissue regeneration, involved in skin inflammatory disorders	Suppress immune responses including inflammation, and graft-versus-host disease	Regulate antigen-specific B-cell immunity
Cell surface receptors	CCR1, CCR5, CCR3, IFN γ -R1, IFN γ -R2	CCR3, CCR4, CCR8, CXCR4 IFN γ -R1, IFN γ -R2	IL-1RI L-21R, IL23R, TGF β RII	TGF β RII, IL17RB	CCR4, CCR10, CCR6, TGF β RII	CD62L/L-selectin, CD25, OX40/CD134	PD-1, CXCR4, CXCR5, ICOS, CD40L, IL-6R α

Fig. 2.3 Perivascular lymphoid infiltrate as a beginning of trafficking of lymphocytes (SALT early pattern)



Antigen-Presenting Cells

A skin-associated lymphoid tissue (SALT) develops (Fig. 2.3). This pattern resembles the distribution of neoplastic skin lymphoid infiltrates. SALT initially are composed of T cells that are attracted to Langerhans cells, the epidermal sentinel immune cells, which are also epidermal antigen-presenting cells. It is postulated that Langerhans cells contribute or perhaps initiate the pathogenesis and recruitment of the malignant T cells in the skin, particularly in mycosis fungoides (Edelson 2001; Berger et al. 2002).

Cytology

A small population of reactive T cells, upon stimulation with certain antigens, demonstrate small cell cerebriform nuclear morphology. Anti-CD3 stimulation is one such trigger (Reinhold et al. 1994). Ultrastructural and monoclonal antibody analysis shows that a normal subset of peripheral blood cells have a cerebriform appearance (Matutes et al. 1983). In practice, less than 3 % of epidermal or dermal T cells have cerebriform nuclei. Although genetic lesions are known to be correlated with blastic transformation of these small cells, certain mitogens/antigen triggers in vitro also appear to cause blastic cytologic

transformation of neoplastic cerebriform cells (Kadin et al. 1984).

Dermis: Generation of Nodular Infiltrate

Subsequently, lymphocytes primed within the epidermis accumulate in the dermis around dermal postcapillary venules and dendritic cells, likely leading to nodular and sometimes diffuse dermal lymphoid infiltrates. Recruitment and help from circulating B cells and Thf cells also come into play. B cells are seen early around capillaries and venules, then later form follicles containing germinal centers composed of B cells, with scattered follicular T helper (Tfh) cells. These cells accumulate in the T-cell ridge between the mantle and light zone. These cells, unlike the interfollicular T cells, coexpress several follicle center associated markers including CD10, Bcl-6, PD1, and CXCL13. Lymphomas arising from this subset tend to form nodules in the dermis with the expression of CD3 plus the aforementioned Tfh subset markers. Angioimmunoblastic T-cell lymphomas, primary cutaneous small- and medium-sized T-cell lymphomas, and some PTCL not

otherwise specified (NOS) have been reported to express these markers. See Chap. 10 for further discussion.

NKT Cells and Gamma-Delta T Cells

Gamma-delta T and NK cells respond to stress-associated factors and are present in the normal epithelial tissues as well as in normal human dermis. They are well-known effectors of the immediate immune response but also have other unique surveillance abilities. These cells express receptors for homing to non-inflamed skin as well as surface receptors for the recognition of allogeneic tumor cells and are reported to be part of the immune surveillance for the elimination of cutaneous tumors and distressed cells (Ebert et al. 2006).

T-Cell Reaction Followed by Accumulation of B Cells

Memory T cells expressing alpha-beta appear to be a major component of skin tropic cells with immune surveillance against previously encountered antigens (Schaerli et al. 2004). Hence, repeated stimulation of skin may induce accumulation of alpha-beta T cells along with NK and gamma-delta T cells.

In vivo findings support this accumulative cellular migration sequence with a dominant CD4+ effector T-cell subset reaction (Fuhlbrigge et al. 1997; Kupper and Edelson 1987; Hoeller et al. 2009) in the epidermis and into the dermis. These CD4+ T cells migrate from dermal venules and infiltrate between bundles of dermal collagen fibers to form nodules within the dermis (Matheu et al. 2008). Two-photon microscopy studies, which allow imaging of movement of live cells, indicate a defined sequence of cell populations trafficking to the skin from draining lymph nodes. This trafficking is more conspicuous among CD4+ T cells than CD8 T cells (Gebhardt et al. 2011). B-cell transition is slower than T-cell migration (Gebhardt et al. 2009; Mackay et al. 1988; Wakim et al. 2008; Tomura et al. 2008).

Pathogens and Dendritic Cells

The expansion of T helper subsets into defined Th1, Th2, or Th17 profiles appears to be induced

by specific types of pathogens. Th1 cells function in autoimmunity and immune response to intracellular pathogens. They secrete IFN-gamma. Th2 cells, which deal with extracellular parasites and are also active in allergy and asthma. Th17 cells provide immunity against a variety of extracellular pathogens, including bacteria such as *Klebsiella pneumoniae* and fungi such as *Cryptococcus neoformans* and *Candida* (Pelletier et al. 2010). The Th17 axis is active in the pathogenesis of a range of dermatological diseases including allergic contact dermatitis, atopic dermatitis, psoriasis, and scleroderma (Asarch et al. 2008).

Th17 and MF

There is limited evidence of Th17 differentiation of tumor cells in mycosis fungoides, particularly in cases with accumulating neutrophils (Ciree et al. 2004) or with a higher rate of progression to advanced stages (Litvinov et al. 2010).

Epithelioid Histiocytes and Granulomas

Epithelioid histiocytes and tissue macrophages aggregate as discrete clusters within the dermis or subcutaneous tissue as granulomas. These arise as an immune system response to an antigen, in which epithelioid macrophages and inflammatory and immune effector cells accumulate. Chronic granulomas are often surrounded by fibrosis or a lymphocyte cuff, but early formation appears as microgranulomas or lymphohistiocytic clusters. Presence of granulomas is often equated with infections, but a variety of noninfectious triggers should also be kept in mind such as autoimmune disorders including rheumatoid skin nodules, Churg-Strauss syndrome, or iatrogenic injections, vaccinations, and lymphoproliferative disorders. Among the latter is a granulomatous form of mycosis fungoides, which can be associated with slack skin.

Histiocytosis arising from tumors of antigen-presenting cells as well as those common in children should also be considered in the proper setting. See discussion in Chap. 14 of histiocytic lesions of the skin.

Subcutaneous Tissue

The subcutaneous tissue or hypodermis is composed of fat and blood vessels. Commonly involved by transformed and diffuse lymphomas, it is seldom inflamed except in certain types of panniculitis. See Chap. 11 for discussion.

The deep vascular plexus is located just above this layer and seldom is involved by perivascular lymphoid infiltrates. In contrast, the superficial vascular plexus just beneath the epidermis is often the site of inflammatory T-cell reactions in dermatitis and psoriasis (Kunstfeld et al. 1997; Lechleitner et al. 1999). Changes in endothelial structure and acquisition of addressins facilitate skin homing above the subcutis (Lechleitner et al. 1999). Gamma-delta T cells and their malignant counterparts can be partially localized to the panniculus (Magro and Wang 2012). The less frequent skin epithelial localization of these cells and their rela-

tive lower density compared to alpha-beta T cells are well recognized (Hocker et al. 2012).

Immunohistochemistry Panel for Evaluation of Lymphohematoporetic Cutaneous Diseases

An immunohistochemical panel is often used in the evaluation of lymphohematopoietic cutaneous diseases. Here we list the commonly used antibodies and show their normal tissue cross-reactions in addition to the usual targets. See list of commonly used antibodies in Table 2.2 and illustrations demonstrating their usefulness in cutaneous hematopathology (Figs. 2.3, 2.4, 2.5, 2.6, 2.7, 2.8, 2.9, 2.10, 2.11, 2.12, 2.13, 2.14, 2.15, 2.16, 2.17, 2.18, 2.19, 2.20, 2.21, 2.22, 2.23, 2.24, 2.25, 2.26, 2.27, 2.28, 2.29, 2.30, 2.31, 2.32, 2.33, and 2.34).

Table 2.2 Antibodies routinely used in paraffin-embedded tissue in the investigation of cutaneous lymphoma/leukemia

Antibody/reactivity	Main specificity	Uses	Normal skin and other reactivities
CD1a membrane	Langerhans cells and cortical thymic T cells (positive in some cases of precursor T-ALL)	Useful in investigating Rosai-Dorfman disease and other histiocytosis or T lymphoblasts but not routinely used for mature T-cell neoplasms. Reacts with dermal dendritic antigen-presenting cells and epidermal Langerhans cells	Langerhans cells
CD2 membrane	Pan T-cell marker, cortical and late thymocytes, and NK cells, antigen-presenting cells	For both NK and T cells, immature and mature	Langerhans cells. Mast cells, some AML and some B-lineage neoplasms
CD3 cytoplasmic/membrane	Pan T-cell marker, late thymocytes, and mature T cells. Expressed on many neoplasms of mature T cells	Mature T-cell marker that may be lost in T-cell lymphomas. Highlights nuclear cerebriform cell morphology Precursor T cell positive	Epsilon chain of the CD3 molecule and shows cytoplasmic positivity in NK cells
CD4 membrane	T-cell helper subset, expressed as weaker staining on monocytes and macrophages	Useful in MF and T-cell lymphomas and for CD4/CD8 ratio	Monocytes, macrophages, histiocytes
CD5 membrane	Pan T-cell marker, expressed by B cells in B-CLL, mantle cell lymphoma	Most of reactive T cells but may be lost in T-cell lymphomas. Absent in most cutaneous marginal zone and cutaneous large B-cell lymphomas	Secondary DLBCL may express CD5 in 1/5, also in secondary splenic marginal zone lymphoma, CLL, and mantle zone lymphoma
CD7 membrane	Pan T-cell marker also in NK cells	Useful in T-cell lymphoma, commonly lost on Sezary cells but not specific	Positive on blast cells in a minority of cases of myelomonocytic leukemia

Table 2.2 (continued)

Antibody/reactivity	Main specificity	Uses	Normal skin and other reactivities
CD8 membrane	T-cell cytotoxic subset. Expressed in some T-cell precursor leukemia/lymphoma	Useful in CD4/CD8 ratio, some CD8-positive cutaneous lymphomas and pagetoid variant of lymphomatoid papulosis	Large granular lymphocytic leukemia, T-CLL/T-PLL, and some gamma-delta T-cell lymphomas may express CD8
CD10 membrane	Common ALL antigen. Expressed by mature and precursors cells. Also in normal germinal center B cells and some normal B-cell precursors such as hematogones	Useful in cutaneous follicle center cell lymphoma but often weaker than Bcl6; also in angioimmunoblastic T-cell lymphoma and precursor B-lymphoblastic lymphoma/leukemia; some peripheral T-cell lymphoma, unspecified	Reacts with normal germinal centers in marginal zone lymphoma Secondary diffuse large B-cell lymphoma or Burkitt lymphoma Cutaneous stromal cells and nonspecifically to ischemic and infarcted lymphoid cells
CD11c membrane	Monocytes, NK cells, and neutrophils	Less commonly used in the skin but may be useful in suspected secondary lymphomas	Seen in hairy cell leukemia, some variant hairy cell leukemia, splenic marginal zone lymphoma, and some cases of CLL and B NHL
CD15 membrane	Neutrophils and myeloid precursor cells, macrophages	Useful in granulocytic sarcoma workup to determine myeloid maturation	Expressed on Reed-Sternberg cells, some large T-cell lymphomas, and rare DLBCL. Some cases of AML and B-cell precursor leukemia
CD20 membrane, cytoplasmic aberrantly in transformed	B-cell antigen	B cells; useful in getting a CD20:CD3 ratio; may be lost in rituximab-treated cases	B cells as well as nodular lymphocyte predominant Hodgkin lymphoma, some precursor B-cell tumors, some plasma cell myeloma
CD23 membrane, dendrites	Activated B cells; follicular dendritic cells	Useful in getting the pattern of germinal centers; disorganized in atypical/transformed germinal centers and lymphoma in skin	Follicular dendritic cell sarcoma; secondary CLL, some follicular lymphomas and diffuse large B-cell lymphoma
CD25 membrane	IL-2 receptor (alpha chain) on T cells and B cells	Detects an activation antigen that may be present on CTCL, LyP and transformed T- or B-cell lymphomas	Adult T-cell leukemia and anaplastic large cell lymphoma and others like hairy cell leukemia, a target antigen of Ontak
CD30 membrane cytoplasmic	Activated T and B lymphoid cell marker	Useful in CD30-positive lymphomas including lymphomatoid papulosis, cutaneous and systemic anaplastic large cell lymphoma and reactive CD30 + skin lesions like scabies, etc.	Expressed in Reed-Sternberg cells and Hodgkin cells in classical Hodgkin lymphoma, embryonal carcinoma, malignant melanoma cells, diffuse large B-cell lymphomas of mediastinal B-cell lymphoma, plasmablastic lymphomas or some myeloid leukemias
CD34 membrane cytoplasmic	Stem cells such as myelolymphoid blasts or normal vessels	Some blastic myeloid leukemia presenting as cutaneous myeloid sarcoma	Cutaneous endothelial cells and may be seen in some vascular skin tumors
CD35 cytoplasmic	Follicular dendritic cell marker	Cutaneous involvement of follicular dendritic cell sarcoma	Some AML, especially with monocytic differentiation
CD43 membrane	Normal T cells, myeloid cells	Useful in a panel of CD3, CD20, and CD43. Positive on myeloid sarcoma (chloroma) in a CD3-negative CD4-positive manner	Also in T-cell lymphomas, ALCL, and some low-grade lymphomas and proportion of diffuse large B-cell lymphoma

(continued)

Table 2.2 (continued)

Antibody/reactivity	Main specificity	Uses	Normal skin and other reactivities
CD45 membrane	Leukocyte common antigen (LCA)—pan hematopoietic marker	Useful in determining if lesion is either lymphoid or leukemic or is a sarcoma, melanoma, or carcinoma	Reacts with mature and immature B, T, myeloid cells and weakly with monocytes
CD45R0 membrane	Activated or memory T cells	Most mature T-cell lymphomas and CTCL derived from memory T cells	Many T-cell lymphomas
CD45RA membrane	Naive B or T cells	Lymphocytes before antigen activation	
CD56 membrane	NK cell marker; also stains a subset of T cells, myeloid cells	Some cutaneous NK or T-cell lymphomas and gamma-delta T cells Subtyping of myeloid sarcoma if CD4 + CD56+ blastic dendritic neoplasm	Also carcinomas such as neuroendocrine derived, some plasma cell myeloma. Some AML, mainly AML-M5. NK LGL leukemias and some T-cell LGL leukemias and extranodal NK/T-cell lymphomas
CD57 membrane	NK cell and T cells	Useful in follicle T helper cell, some NK cell large granular leukemia	Large granular lymphocytic leukemia, NK cells
CD68 cytoplasmic	Histiocytes, monocytes, and macrophages	Useful in myelomonocytic sarcoma, cutaneous Rosai-Dorfman disease, Langerhans cells and tissue macrophages	Some cells of granulocytic lineage, positive in granulomas
CD79a membrane	B cells, plasma cells	Useful in cases with lost CD20	May be expressed by some AML with aberrant B-cell antigens, staining both B and plasma cells
CD117 cytoplasmic	Stem cells, melanoblasts Melanocytes	Useful in the skin for determining loss of melanocytes	Epidermal melanocytic cells, adnexa, and in leukemia for the presence of blasts
CD123 membrane	Detects the alpha chain of the IL3 receptor	Expressed in plasmacytoid dendritic cell neoplasm and normal plasmacytoid dendritic cells	Also in NK cells, eosinophils, basophils, and monocytes; hairy cell leukemia, about half of AML and precursor B-lymphoblastic lymphoma
CD138 cytoplasmic membrane	Expressed in plasma cells and epithelia	Myeloma, plasmablastic lymphoma, plasma cells, primary effusion lymphoma, and some lymphoplasmacytic lymphoma	Normal and neoplastic epithelia
CD163 membrane	Hemoglobin scavenger receptor glycoprotein	Expressed on monocytes and macrophages and in cutaneous Rosai-Dorfman	Positive in myelomonocytic leukemia and histiocytic malignancies
CD279 (PD1) membrane	Programmed death 1 T cells, T follicle T helper cell	Expressed in both CTCL and PTCL, NOS, and in lymphomas such as AITL with helper T-cell origin	Positive in normal germinal center T cells
BCL2 cytoplasmic membrane	Apoptosis regulator	Not expressed in reactive follicle centers; seen in follicular lymphomas and DLBCL, leg type	Also stains a wide range of normal and neoplastic T cells, both inside and outside follicles
BCL6 nuclear	Transcription factor	Positive in follicular lymphoma and in a subset of diffuse large B-cell lymphoma	Also positive in nuclei of normal germinal center cells and epithelia, pattern useful in determining the organization of germinal centers
BOB-1 nuclear	Lymphocyte transcription cofactor	Marks L and H cells in nodular lymphocyte predominant	Germinal center cells Negative in RS-cells of classic Hodgkin lymphoma

Table 2.2 (continued)

Antibody/reactivity	Main specificity	Uses	Normal skin and other reactivities
Cyclin D1 nuclear	Transcription factor	Mantle cell lymphoma versus other lymphomas	Some cases of plasma cell myeloma and hairy cell leukemia Epithelia reactivity in normal tissue
EBV-LMP1/EBER ISH Cytoplasmic/ nuclear	Epstein-Barr virus	Useful in extranodal NK T cell and posttransplant lymphomas	
Factor XIIIa nuclear	Histiocytes and dermal dendrocytes	Useful in distinguishing dermal dendritic cells from lymphomas	Normal dermal dendrocytes
Granzyme B cytoplasmic	Granulysin or cytotoxic granules of cytotoxic effector cells	Cytotoxic T-cell marker in CD8 or cytotoxic lymphomas; one half of LyP, advanced stage mycosis fungoides, increased in lymphoid hyperplasia	Some T-cell lymphomas especially of LGL or cytotoxic NK T-cell origin
IRF4 (MUM1) nuclear	Multiple myeloma 1 MUM1/IRF4 expressed in post-germinal center B cells including leg type of DLBCL. Often coexpressed with CD30 in ALCL and LyP	Regulator factor protein, B-cell proliferation/differentiation marker	Prognostic marker in nodal DLBCL
Kappa Lambda ISH or IHC cytoplasmic	Light chains	Useful in determining clonal restriction in plasma cells; may be useful in cutaneous B-cell lymphomas, especially marginal zone lymphoma	May not react to neoplastic B cells despite expression in nonneoplastic plasma cells in the background
Ki67/MIB1 nuclear	Proliferative marker surrogate for DNA synthesis	Useful in determining the proliferative activity and grading of cutaneous lymphomas	High in aggressive versus low in low-grade lymphoma, cross-reacts with proliferating epithelia e.g., basal layer keratinocytes
Herpes simplex virus 2	Immunostains HSV2	Useful in workup of herpes-induced pseudolymphoma	
Myeloperoxidase cytoplasmic	Granulocytes and some monocytes	Granulocytes cell marker (mature myeloid cells) useful in granulocytic sarcoma positive in most AML	Monocytes with weaker staining than those of granulocytic lineage
CD246 (p80; ALK1) nuclear cytoplasmic	Anaplastic lymphoma kinase-1	Anaplastic large cell lymphoma; ALK+; also ALK cytoplasmic + nuclear usually positive in secondary ALCL and only rarely positive (cytoplasmic) in primary cutaneous ALCL	Large cell lymphoma workup
S100 cytoplasmic	Neuroectodermal marker	Interdigitating reticulum cells and Langerhans cells and Rosai-Dorfman disease	Melanomas, most sarcomas, gamma-delta T cells and Schwann and other stromal cells
TCR β TCR gamma-delta membrane	T-cell receptor subsets	Useful in determining the origin of a subcutaneous or other T-cell lymphomas	Normal T cells in a 9:1 ratio between beta and gamma
TdT nuclear	Terminal deoxyribonucleotidyl transferase	Immature B and T cells as well as myeloid cells	Precursor lymphoblastic leukemia, T or B and some rare AML subtypes

(continued)

Table 2.2 (continued)

Antibody/reactivity	Main specificity	Uses	Normal skin and other reactivities
TIA-1 cytoplasmic	T-cell intracellular antigen 1	Cytotoxic T-cell marker	Positive in some T-cell lymphomas, such as CD8 or gamma-delta T-cell lymphoma and T-cell LGL leukemia
Pankeratin cytoplasmic	Cocktail of AE1, AE3, Cam 5.2	Useful in carcinoma undifferentiated tumor versus lymphoma	Epithelia/keratinocytes
Pax-5	Transcription factor active in early stages of B-cell differentiation	Most B-cell neoplasms, Reed-Sternberg cells, rare ALCL	Useful in the differential diagnosis of undifferentiated neoplasms
EMA	Epithelial membrane antigen	Application in systemic ALCL versus cutaneous ALCL	EMA seen in systemic and not in cutaneous CD30 lymphomas, epithelia, plasma cells

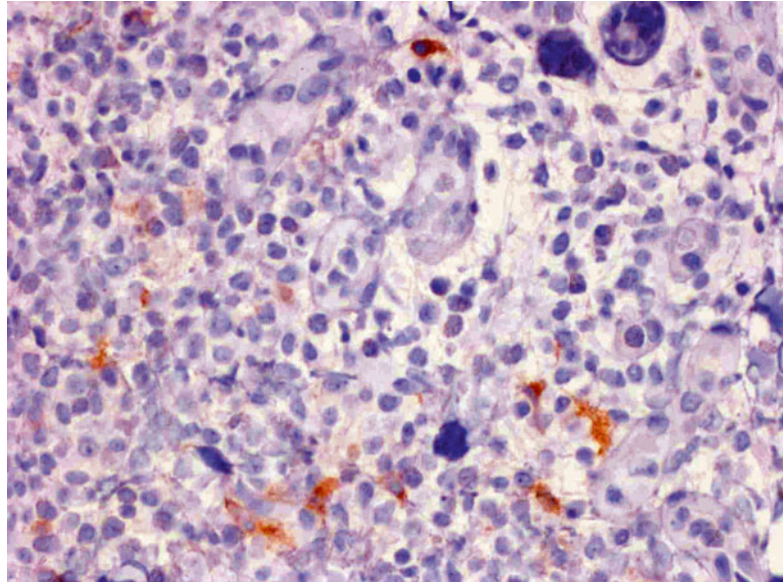
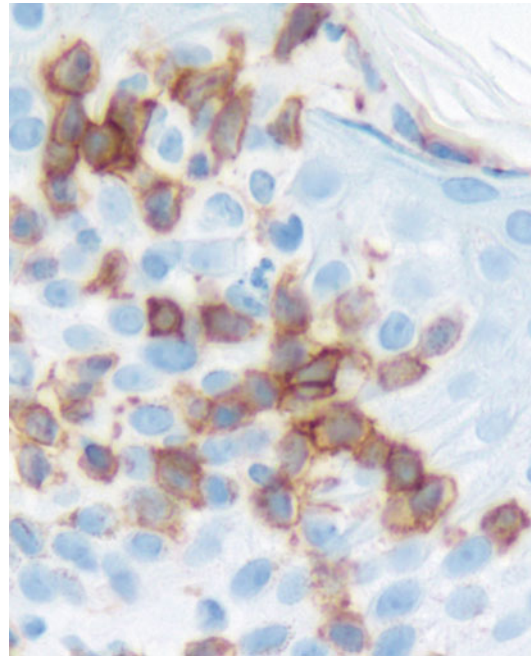
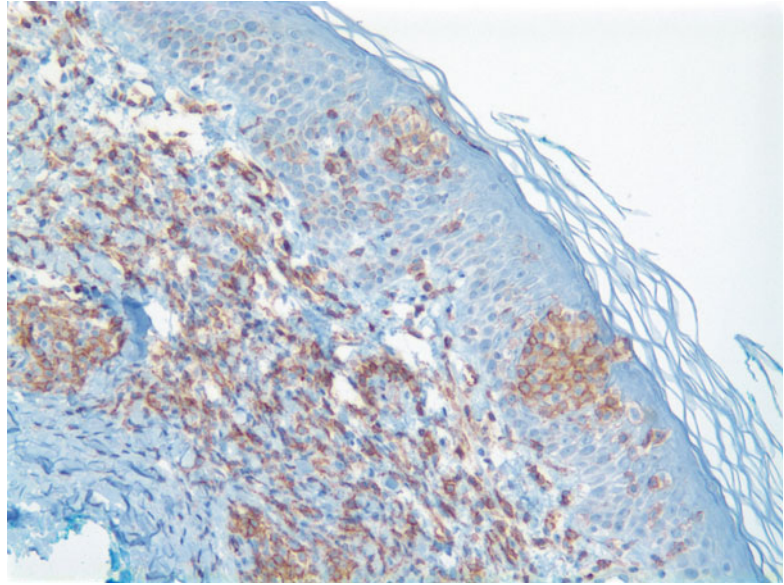


Fig. 2.4 CD1a. High-power view of CD1a brown-stained dermal Langerhans cells with dendritic processes

Fig. 2.5 CD2. Pan T-cell staining on a contact dermatitis as well as with partial staining of CD2 with receptors in Langerhans cell vesicles and with other dermal T lymphocytes



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Fig. 2.6 CD3. Oil magnification view of nuclear contour highlighted by CD3 stain

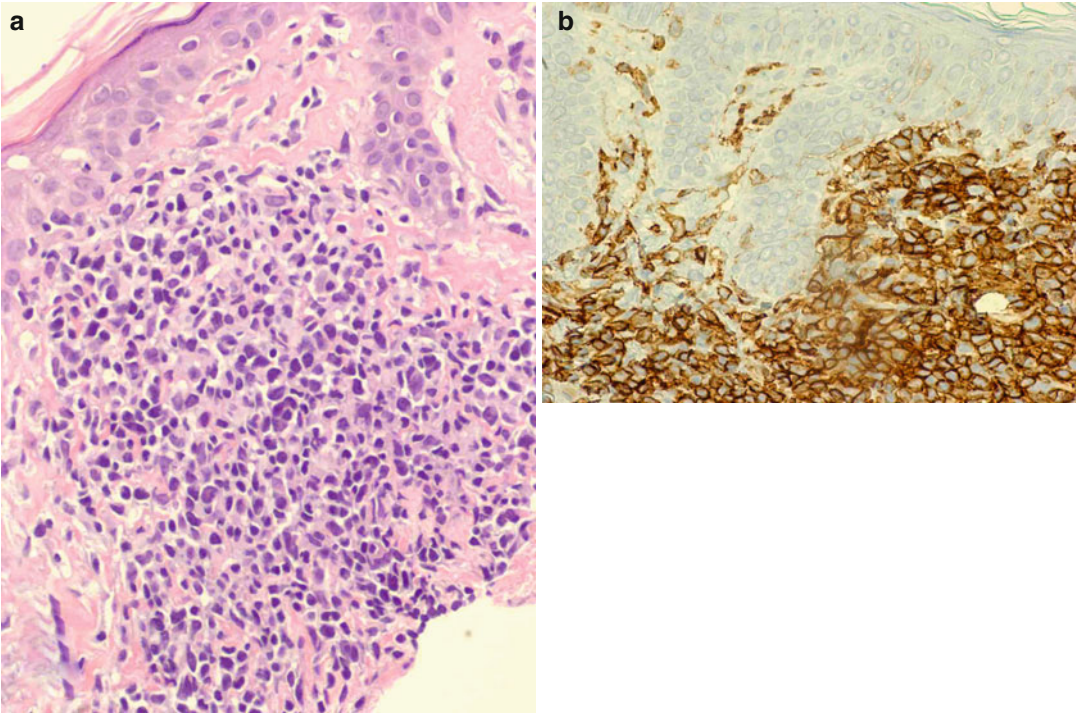


Fig. 2.7 CD4. Histology of solitary cutaneous small and medium T-cell lymphoma with corresponding CD4 immunostaining below

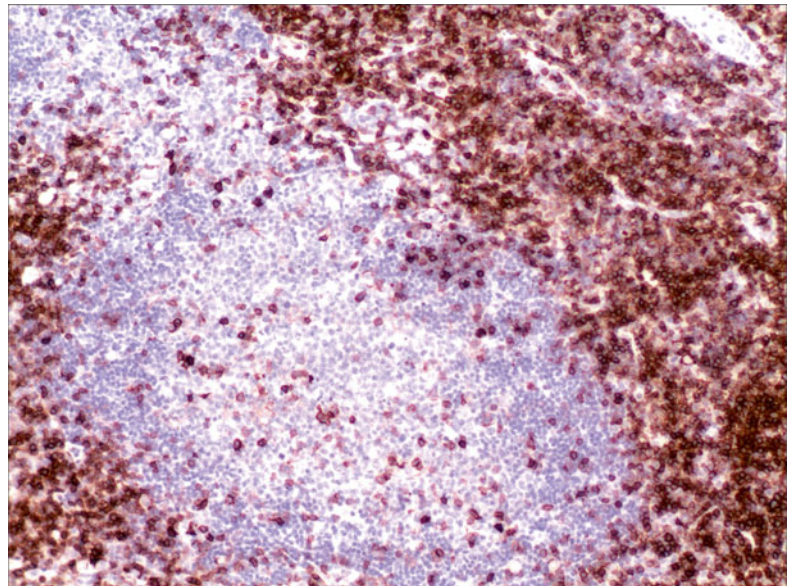


Fig. 2.8 CD5. Staining mostly of interfollicular T cells with partial weaker staining of mantle zone cells and germinal center T cells

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Fig. 2.9 CD7. T cells partly stained with CD7 in a solitary cutaneous small and medium T cell-lymphoma

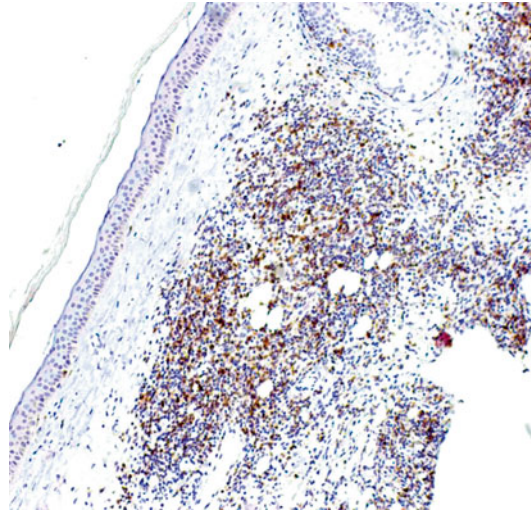


Fig. 2.10 CD8. Dermal CD8-positive T cells in lymphomatous folliculitis secondary to acneiform follicular hair plugging reaction

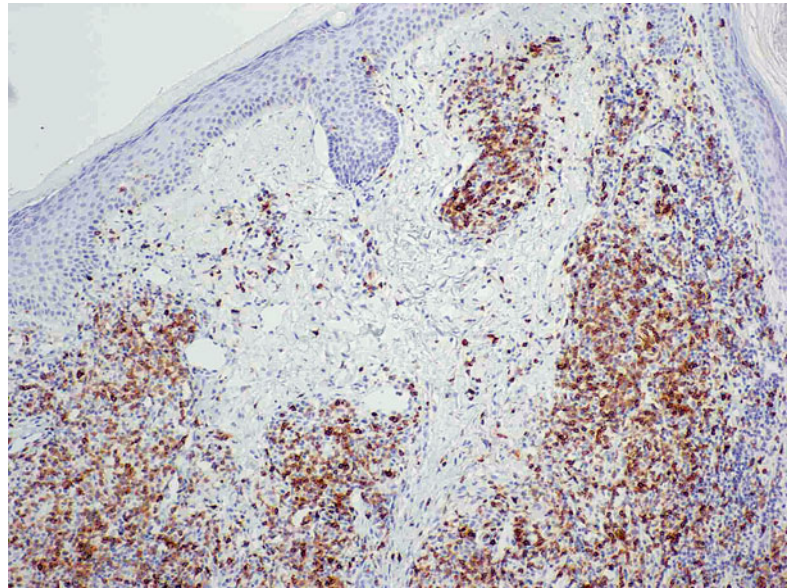


Fig. 2.11 CD10. Stromal fibrous interfollicular pattern of staining of CD10 in cutaneous lymphoid hyperplasia. Note the weaker staining of benign germinal center

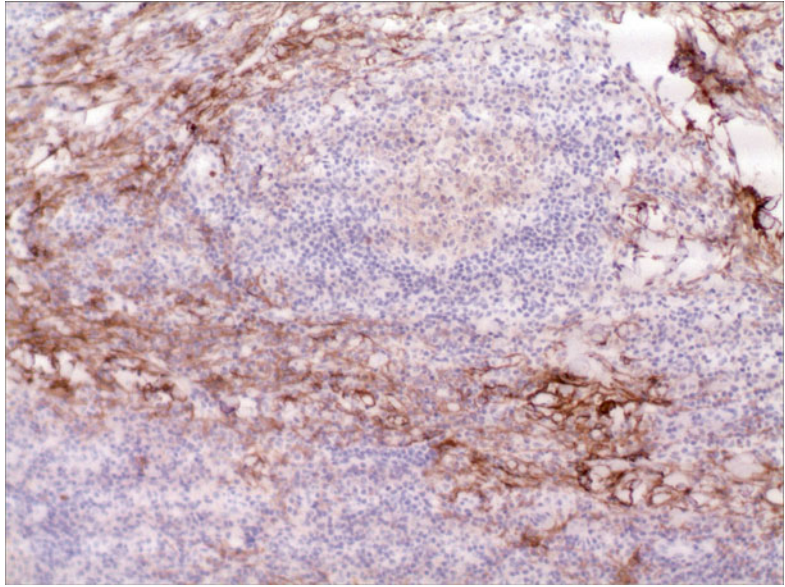


Fig. 2.12 Reed-Sternberg cell stained for CD15; adjacent granulocytes stain diffusely. Reed-Sternberg cells typically are found in the lymph nodes involved by Hodgkin lymphoma, rarely in the skin

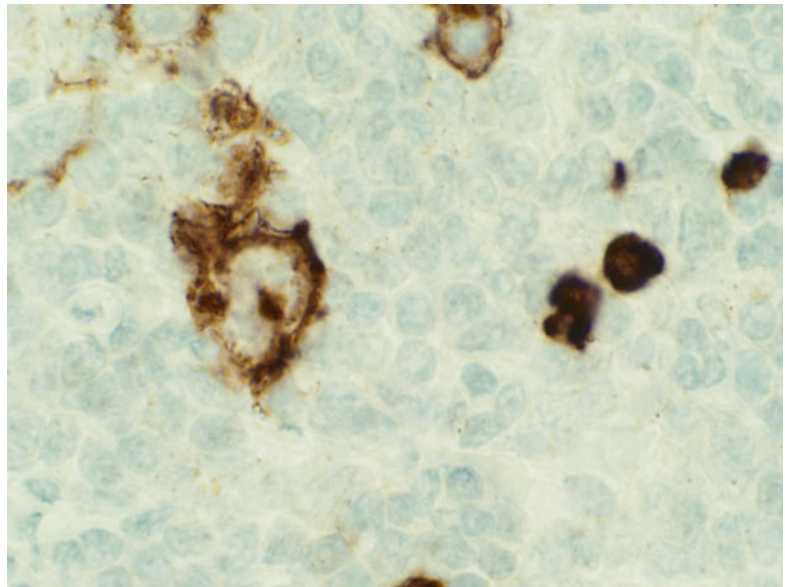


Fig. 2.13 CD20. Normal staining pattern in cutaneous lymphoid hyperplasia with paler staining centers and darker mantle zone lymphocytes separated by nonstaining interfollicular T cells

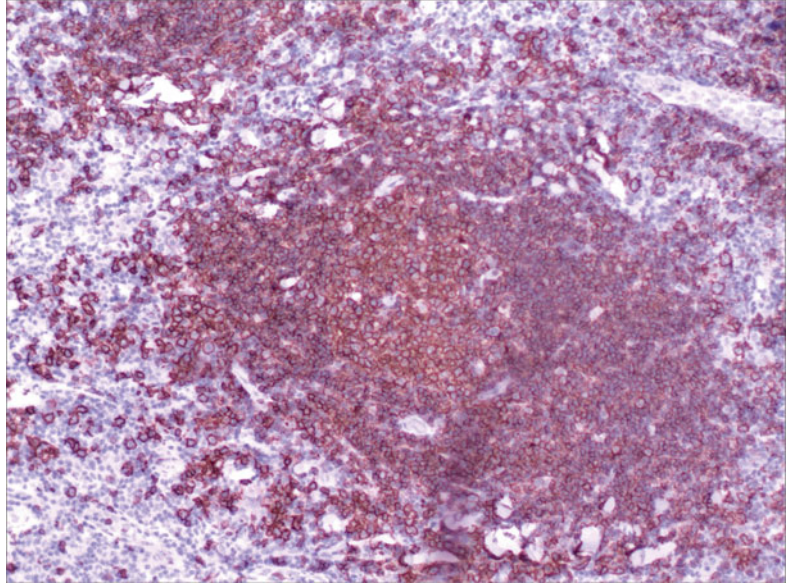


Fig. 2.14 CD23. Dense staining of CD23-positive infiltrate in the skin involved by systemic chronic lymphocytic leukemia that was also CD5 positive and CD20 positive

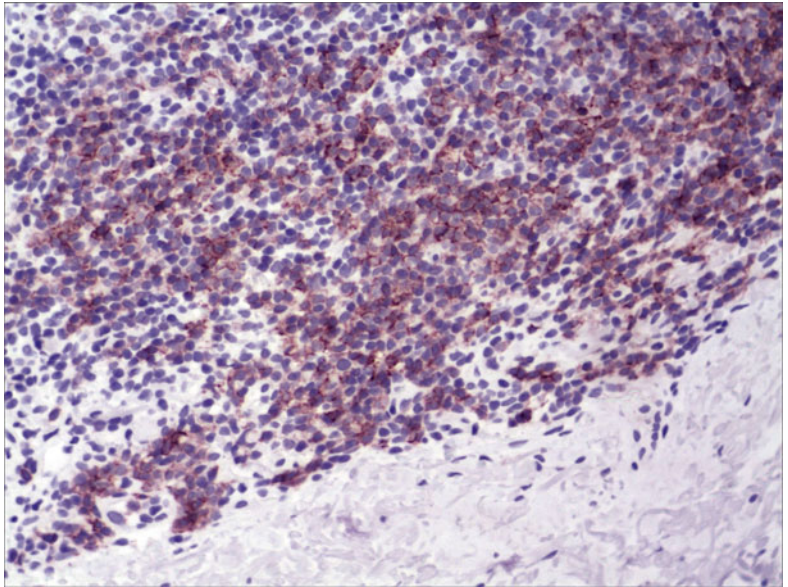


Fig. 2.15 CD30. Typical high-power view of clusters of lymphomatoid papulosis neoplastic CD30 large cells

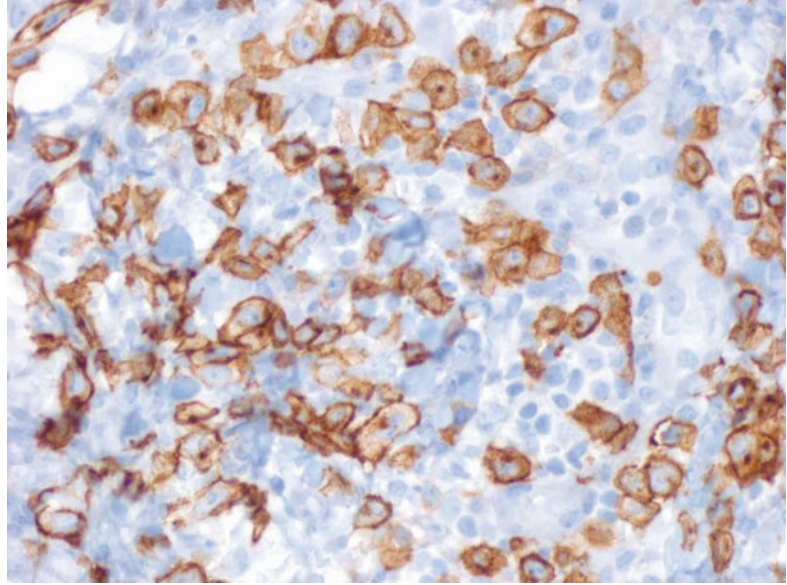


Fig. 2.16 CD34. Vessels and endothelia show as immunoreactive internal control for the evaluation of stem cell blasts in the skin with blastic infiltrate

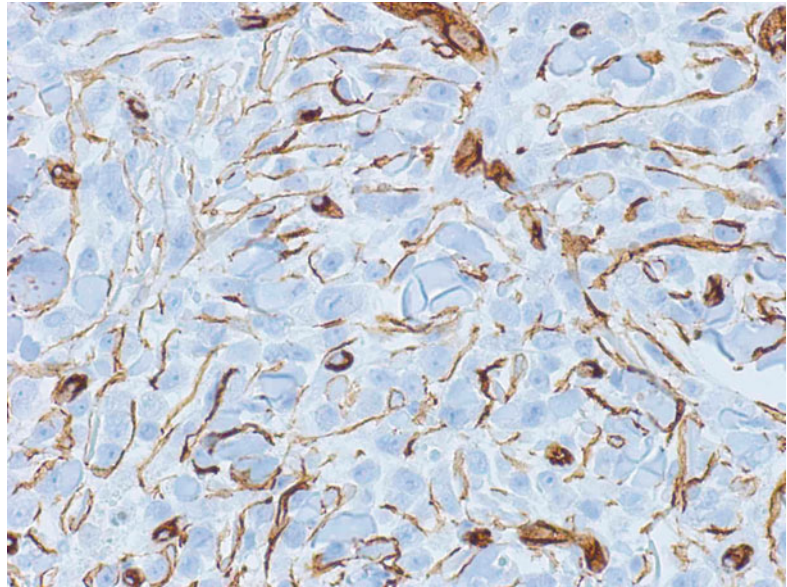


Fig. 2.17 CD43. Sheets of myeloid sarcoma immature cells stained with CD43

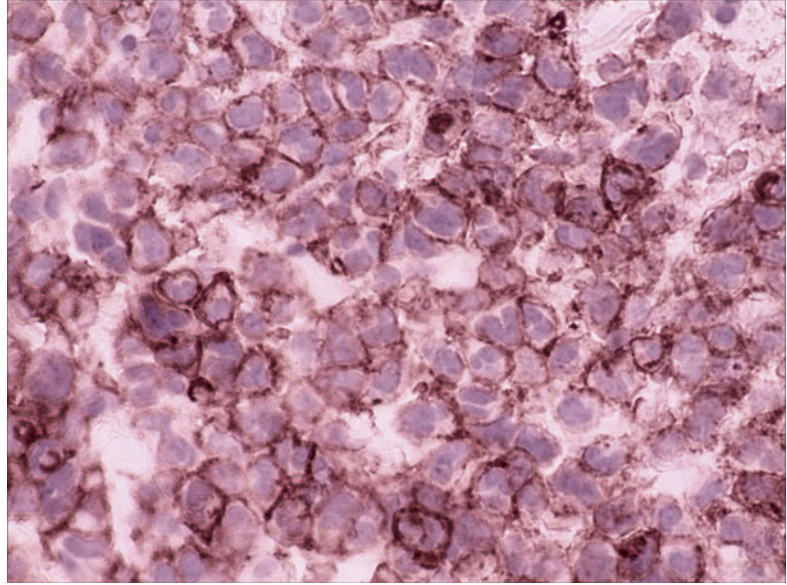


Fig. 2.18 CD45. Leukocyte common antigen (LCA) in myelomonocytic skin infiltrate

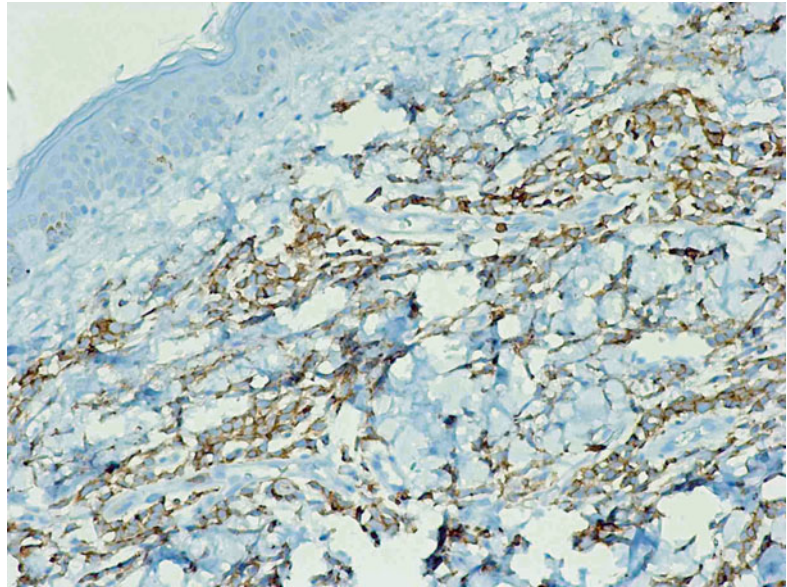


Fig. 2.19 CD56. Single-file blastic infiltrate of a leukemia cutis rare type of blastic plasmacytoid dendritic cell leukemia

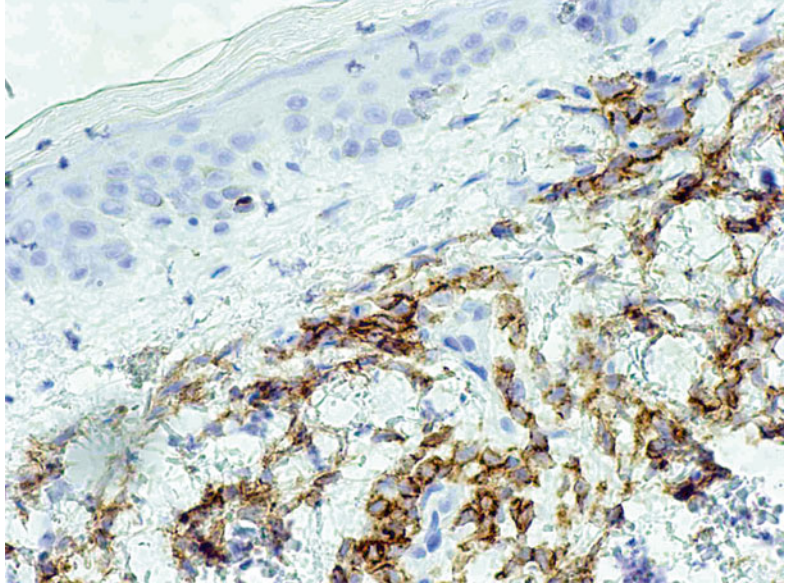
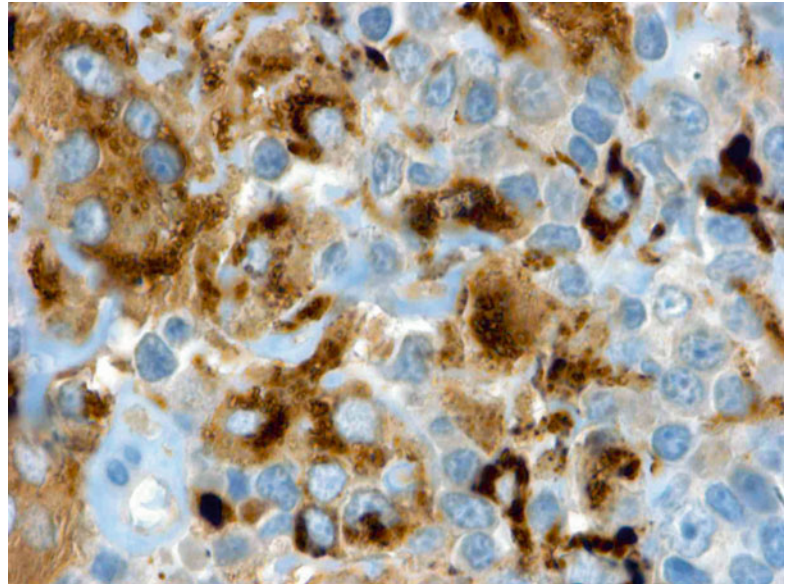


Fig. 2.20 CD68. Large epithelioid CD68 + histiocytes with lymphophagocytosis in cutaneous Rosai-Dorfman disease



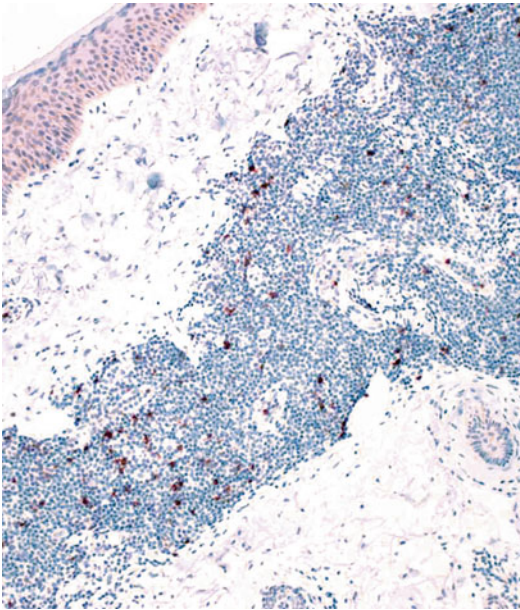


Fig. 2.21 CD79a. Scattered CD79a + B cells and plasma cells in predominantly T-cell nodular infiltrate

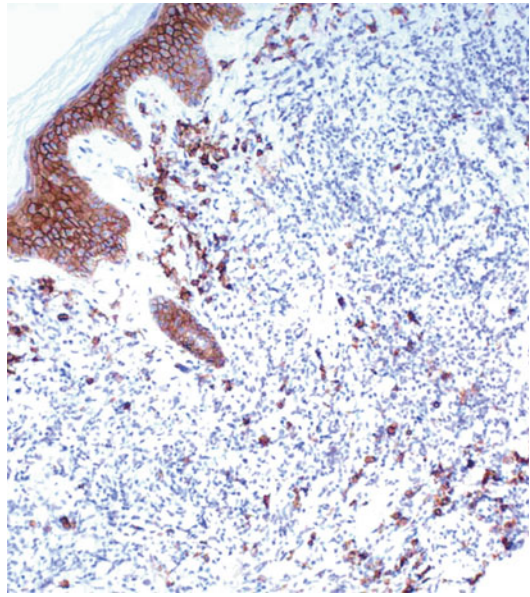


Fig. 2.23 CD138. Dermal plasma cells and epithelia in the skin and dermis stain with CD138

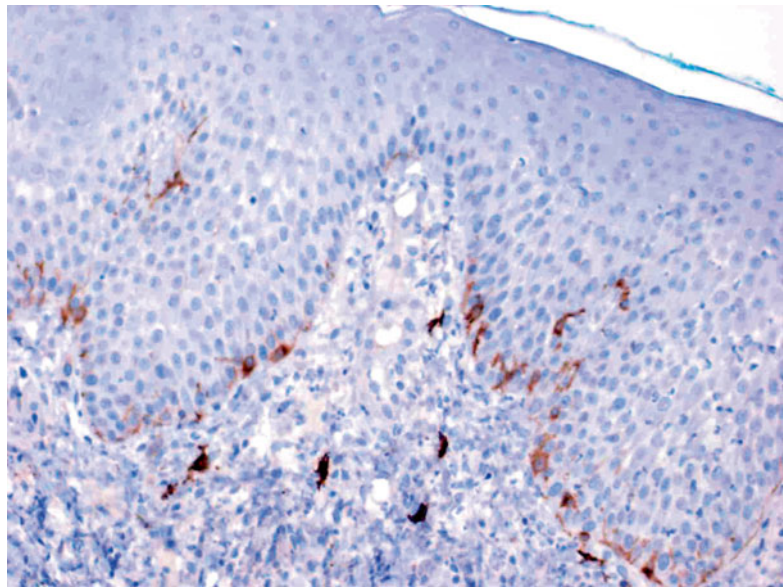


Fig. 2.22 CD117. Melanocytes, melanophages with melanin, and adnexa are CD117 (stem cell factor receptor) typical skin reactivity that may be used to determine pigmentation

Fig. 2.24 CD279 (programmed death 1, PD1). Staining of follicle T helper cell seen in normal germinal centers and useful for determining if a lymphoma in the skin has follicle T helper origin

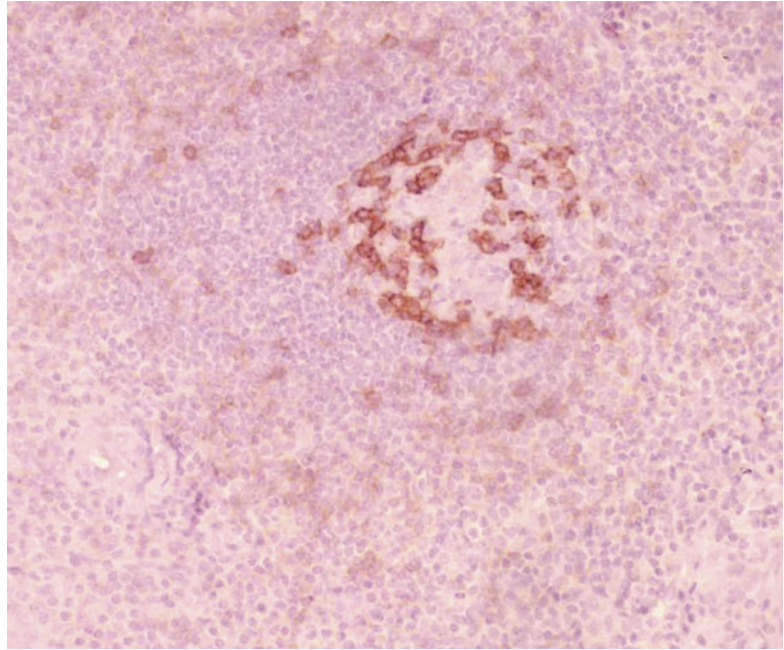


Fig. 2.25 Bcl2. Reactive T cells in and around an atypical cutaneous lymphoid hyperplasia with disorganized germinal centers, same cases as the following Bcl6

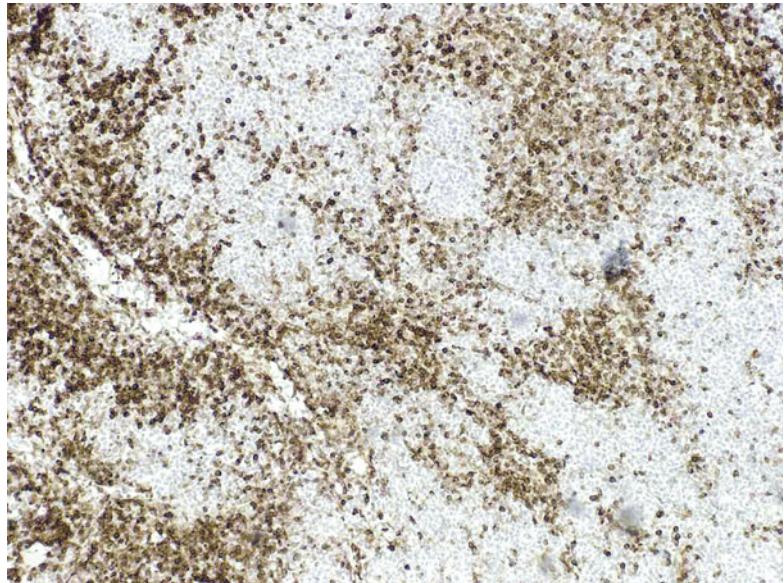


Fig. 2.26 Bcl6. Disorganized germinal centers highlighted by bcl6 nuclear stain

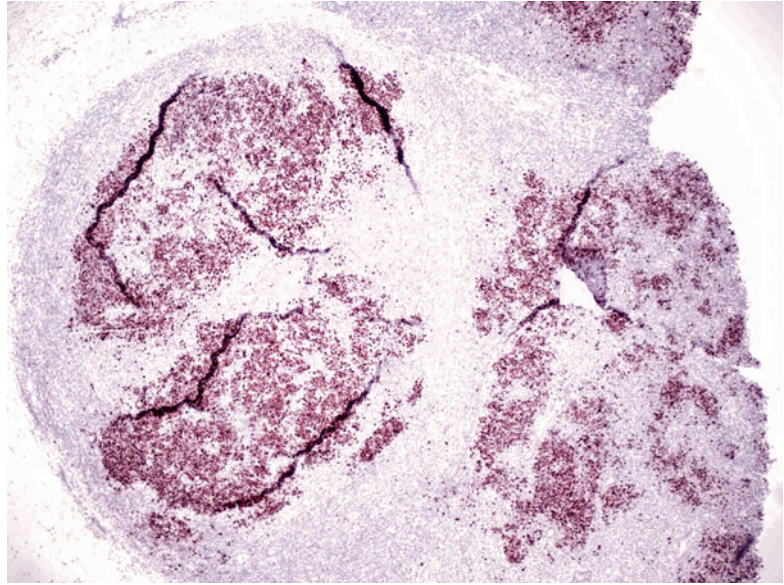


Fig. 2.27 Cyclin D1. Normal tissue reactivity of cyclin D1 (bcl-1) for mantle cell lymphoma showing reactivity to normal endothelial lining tissue and larger darker staining scattered histiocytes. Epidermis weakly stained (not shown)

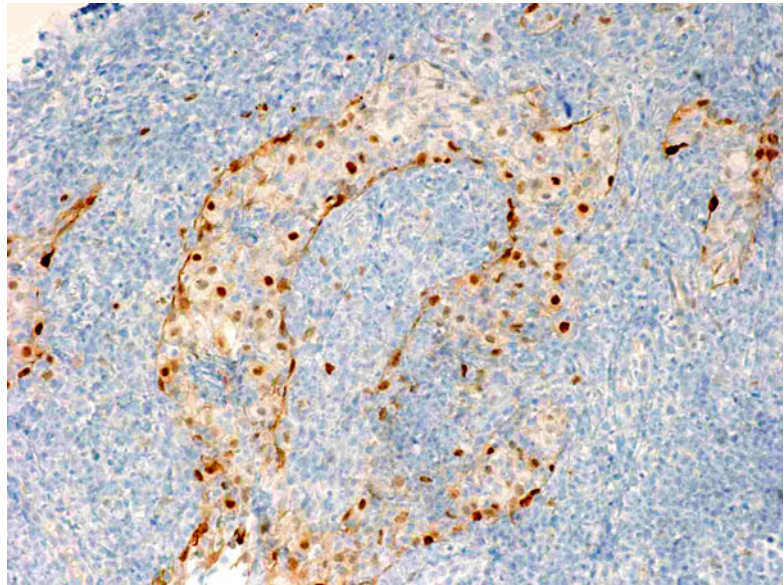


Fig. 2.28 Factor XIIIa. Dermal dendrocytes showing granular cytoplasmic staining of marrow-derived histiocytes, putative origin of fibrohistiocytomas in the skin

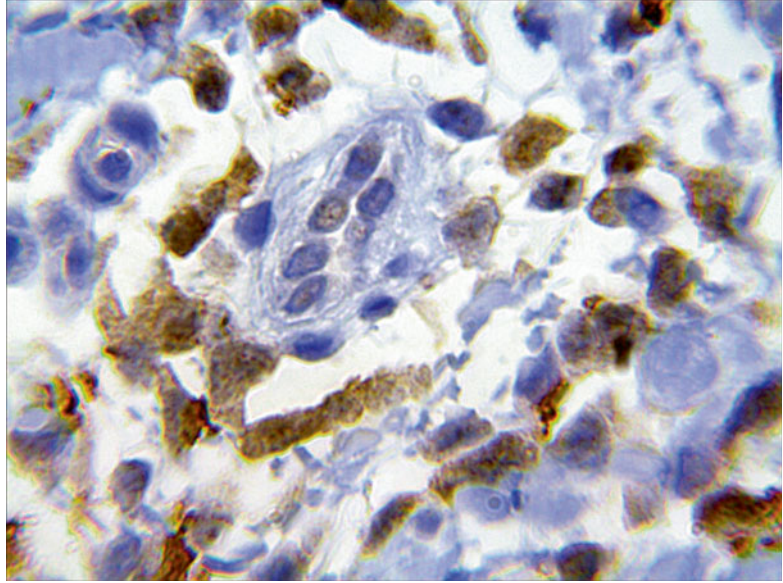


Fig. 2.29 MUM1. Diffuse large B-cell lymphoma, leg type with MUM1 (IRF4) nuclear positivity

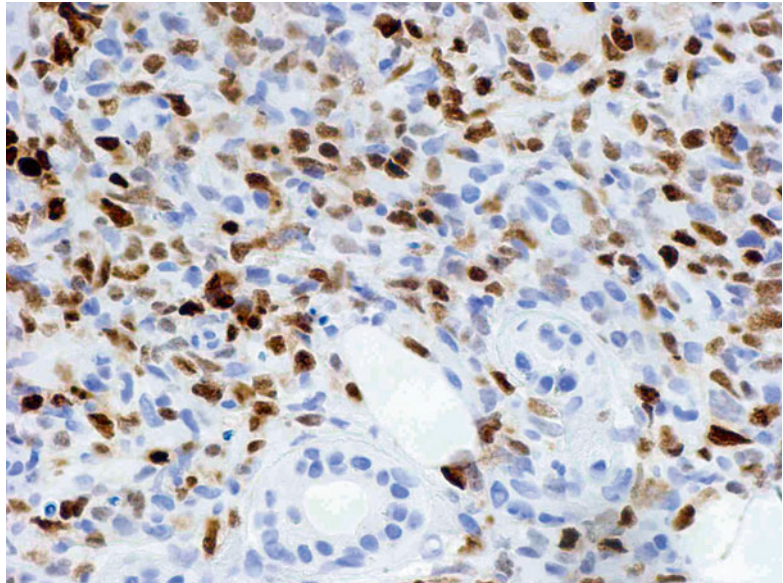


Fig. 2.30 Ki67. Proliferating lymphocytes in the dermis along with few nuclear reactive keratinocytes stained with Ki67

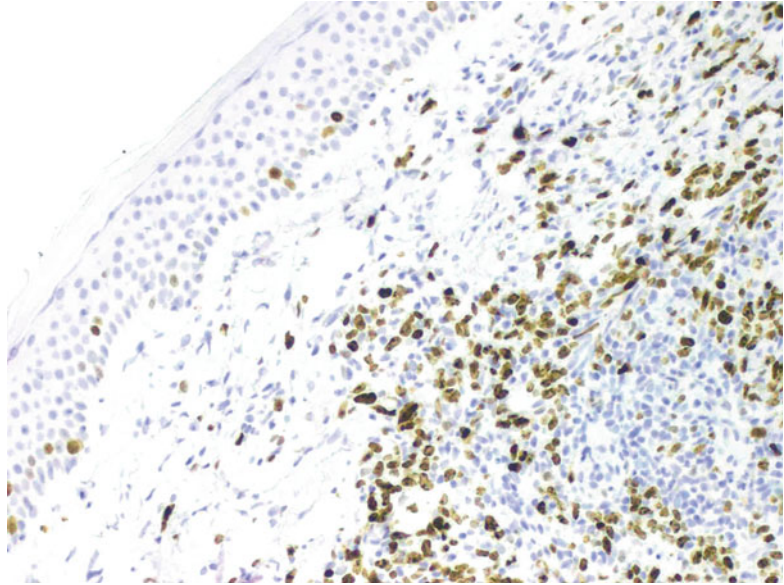


Fig. 2.31 HSV2. Herpes simplex immunostain showing nuclear reactive infected keratinocytes and intense lymphohistiocytic dermal response. Herpes infection is a rare cause of pseudolymphoma

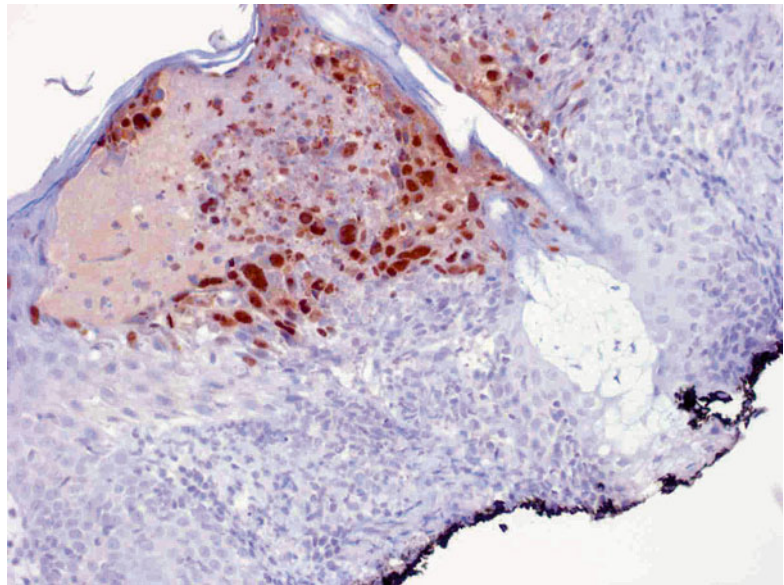


Fig. 2.32 S100. Sentinel cells or epidermal Langerhans cells highlighted by S100b stain

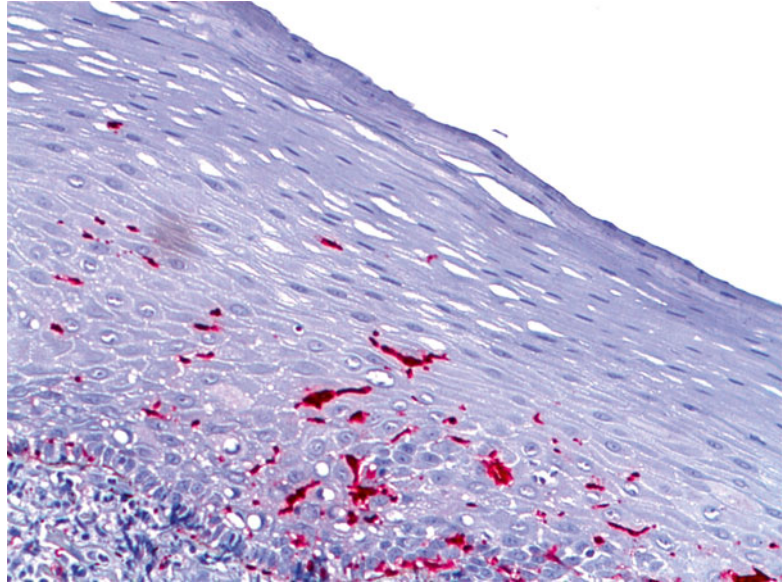


Fig. 2.33 TdT. Lymphoblasts in oil power with TdT nuclear positivity consistent with precursor lymphoblastic leukemia skin involvement

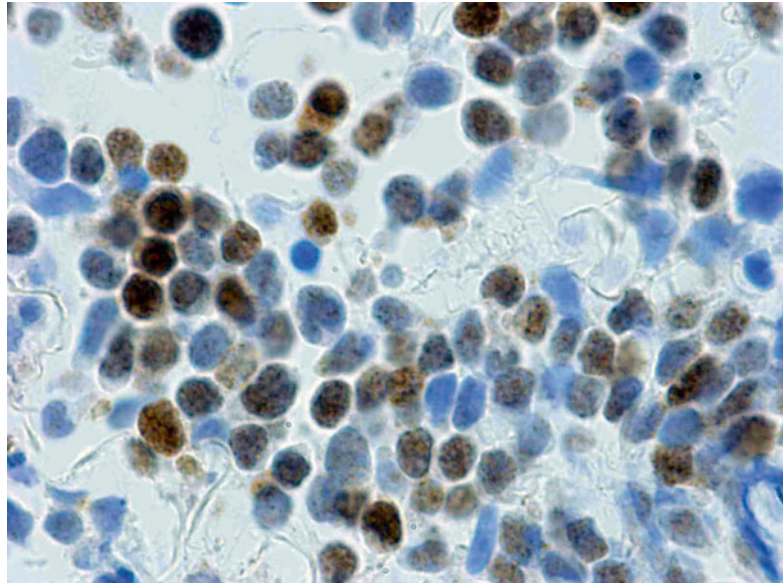
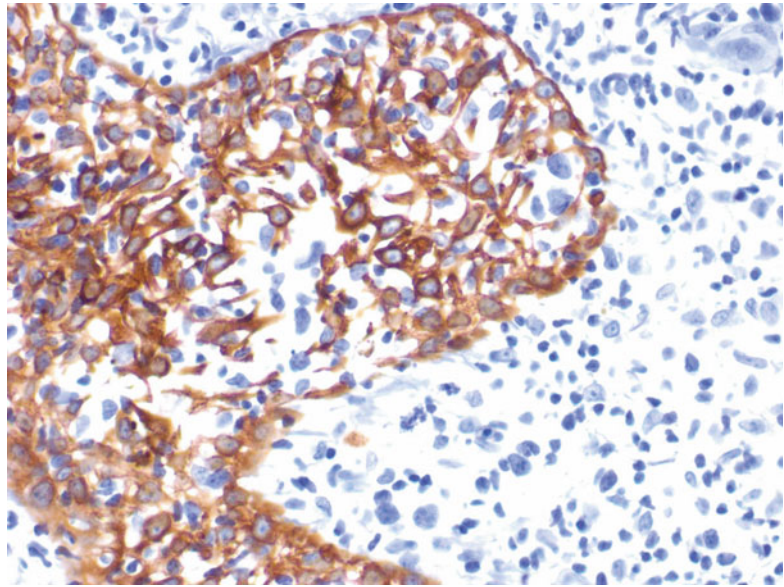


Fig. 2.34 Pankeratin. Highlighted keratinocytes with epidermotropic lymphocytes



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