REVIEW

Functions and Uses of Immunohistochemical Stains in Cutaneous Infiltrates of Hematopoietic Origin: A Review for the Practicing Dermatologist

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Background: **Immunohistochemical stains, particularly those for cutaneous lymphomas, have similar-sounding names, which may lead to confusion among dermatologists who are not well versed in the terminology of the tools used for pathologic diagnosis. Also aiding in this is the fact that some familiar stains are constantly investigated for novel utility in different tumors, and a plethora of new stains regularly emerge in the peer-reviewed literature.**

Objective: **To review the major stains encountered in dermatopathologic reports for cutaneous lymphomas. A select number of other stains are reviewed that are either new and under investigation in several cutaneous processes or have a new use described in recent reports.**

Methods: **The peer-reviewed literature was searched and analyzed for the accepted purposes of using these markers.**

Results: **All pertinent findings for these immunostains are reported with the purpose of educating the dermatology community.**

Conclusion: **This review serves as a reference to clarify potentially confusing immunohistochemical stains.**

Antécédents: **Les marqueurs immunohistochimiques, particulièrement ceux des lymphomes cutanés, portent des noms similaires, ce qui pourrait être source de confusion pour les dermatologues qui ne connaissent pas bien la terminologie des outils utilisés dans le diagnostic des pathologies. S'ajoute à cela le fait que certains marqueurs connus sont constamment essayés pour des usages nouveaux sur différentes tumeurs et une multitude de nouveaux marqueurs apparaissent régulièrement dans les publications scientifiques revues par les pairs.**

Objectif: **Passer en revue les principaux marqueurs qu'on retrouve dans les rapports dermatopathologiques des lymphomes cutanés. Un nombre choisi d'autres marqueurs, soit nouveaux et font l'objet d'enquêtes dans plusieurs processus cutanés ou anciens mais présentant un nouvel usage qui a fait l'objet de rapports récents, seront également révisés.**

Méthodes: **Les publications scientifiques ayant fait l'objet de révision par les pairs ont été fouillées et analysées pour relever les fins acceptables auxquelles ces marqueurs sont utilisés.**

Résultats: **Tous les résultats pertinents à ces marqueurs sont rapportés aux fins d'information pour les dermatologues.**

Conclusion: **Cette revue sert à titre de référence afin de clarifier les marqueurs immunohistochimiques qui pourraient être source de confusion.**

DERMATOPATHOLOGISTS have an abundant variety of immunohistochemical stains at their disposal when trying to diagnose entities that are not readily recognizable when biopsies are examined microscopically after staining with hematoxylin and eosin. These chemicals work by labeling cell markers with antibodies, thus allowing for characterization of cellular expression and function. Whereas dermatopathologists are familiar with the nomenclature, indication for, and utility of these stains, the practicing dermatologist is unlikely to have a thorough knowledge of many of them. Nevertheless, in many cases, the interpretation of these stains when applied to a skin biopsy will often be included in a pathology report. It is therefore important that dermatologists have at least some familiarity with them so that they will be able to understand the significance of a positive or negative result. Although many of the stains are used commonly and are well known, a number of others are more esoteric and less commonly used. In this review, we aim to provide

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an overview of some of the newer immunoperoxidase stains that are becoming more commonly used by dermatopathologists. This review is, however, by no means exhaustive in depth or scope as literally hundreds of such stains and markers are currently in use in pathology, many of which are occasionally applicable to dermatology. For quick reference, a summary has been provided in Table 1.

Immunohistochemical Stains

CD1a

Cluster differentiation group (CD)1a is a member of a glycoprotein family that is expressed on the surface of antigen-presenting cells and certain T-cell populations located within the thymus gland. CD1a functions to present lipid antigens to T cells. Mature T cells in the peripheral blood and lymphoid tissues do not express CD1a.[1,2]

CD1a is classically associated with Langerhans cells, and as such, it is useful in identifying Langerhans cells (Figure 1).[1] Dermal dendritic cells also stain positively.[3,4] CD1a-expressing networks and heavy infiltrates of dendritic cells are seen in B- and T-cell lymphoproliferative disorders and benign inflammatory skin conditions.[4] The presence of such large numbers of antigen-presenting cells in benign and malignant skin infiltrates has led some authors to propose that cutaneous lymphomas arise from a malignant clone that develops through persistent antigen stimulation.[4,5] Expression of CD1a is very important in the diagnosis of Langerhans cell proliferations and Langerhans cell histiocytosis. Along with their characteristic morphology, these cells typically stain negative for lymphocyte markers but positively for S-100 antigen and CD1a. The development and use of CD1a are major advances as, previously, the only way to confirm Langerhans cell differentiation was by demonstration of Birbeck granules using electron microscopy.[6]

CD3

CD3 is an integral component of the T-cell receptor complex found on the surface of mature T cells (Figure 2). Prior to surface localization, in immature T cells, CD3 can be found expressed within the cytoplasm. Given that its function is so integral to the functioning of the T-cell receptor, CD3 is the most T cell–specific immunohistochemical marker.[1]

Because CD3 is expressed on T cells at all levels of maturation, it is not specific for any disease process. However, the proportion of CD3 positivity within a lymphoid infiltrate gives CD3 staining added utility. T-cell lymphomas generally stain strongly and uniformly with CD3.[7] It is also found in lymphomatoid papulosis (LyP), benign lymphocytic infiltrates, and the infiltrating T cells found in B-cell lymphomas. Most cases of LyP contain an abundance of T cells and thus stain diffusely positive for CD3. Benign B-cell pseudolymphomas, in contrast, have a larger percentage of B cells, and B-cell lymphomas usually contain relatively few CD3-positive cells except in some variants, such as T cell–rich B-cell lymphoma.[8–11] Mycosis fungoides (MF) and other T-cell lymphomas may demonstrate a decrease in CD3 expression as well as other T-cell markers, especially in later-stage lesions when evaluated with flow cytometry, although CD3 is generally diffusely expressed by immunohistochemistry in virtually all stages (Figure 3).[11–14] In contrast to some T-cell markers, diminished CD3 expression has been shown to be nonspecific.[15]

CD4

CD4 is a glycoprotein that is expressed in T cells in later stages of maturation (see Figure 2). CD4-positive T cells are also referred to as helper T cells. CD4 functions to activate the helper T cell after antigen-presenting cells stimulate the T-cell receptor with an antigen and is specific for class II major histocompatibility complex proteins.[1,16] CD4 is present in both benign and malignant T cells, so its expression is not specific for any disease.

Most cutaneous T-cell lymphomas such as MF stain prominently with CD4 (see Figure 2).[17,18] However, some cutaneous T-cell lymphomas, including some cases of MF, may have CD4-negative phenotypes, and even CD4-negative/CD8-negative phenotypes have been described. At one time, this ''double-negative'' phenotype was thought to have a worse prognosis, although this has since been disproven.[13,14,19] Folliculotropic MF classically demonstrates a markedly increased number of CD4-positive T cells compared to CD8-positive T cells.[20] CD30-positive lymphoproliferative disorders are mostly CD4 positive/CD8 negative as well.[21] Subcutaneous panniculitis–like T-cell lymphoma (SPTL) is uncharacteristic of most T-cell lymphomas in that it is predominantly CD4 negative.[22,23] CD4 may also be aberrantly expressed by chronic lymphocytic leukemia and acute myeloid leukemias; however, this has no apparent clinical significance.[1,24,25]

Table 1. Immunohistochemical Stains and Their Corresponding Positive Cell Populations and Cellular Proliferations

Immunostain	*Cells Identified*	*Used in*
CD1a	Langerhans cells	Langerhans cell proliferations
	Dermal dendritic cells	Benign inflammatory conditions
		B- and T-cell lymphoproliferative disorders
CD3	T lymphocytes, all stages of development	T-cell lymphomas
		May be lost in mycosis fungoides
		Lymphomatoid papulosis
		Benign lymphocytic infiltrates
CD4	T lymphocytes, late stages of development	T-cell lymphomas
		May be lost in mycosis fungoides
		$CD30^+$ lymphoproliferative disorders
		Aberrant expression in CLL and AML
	NK cells	Benign NK cell proliferations
		Negative in malignant NK cell neoplasms
CD5	T lymphocytes, immature and mature stages of development	T-cell lymphomas
		May be lost in mycosis fungoides
	Some B lymphocytes	Coexpressed with CD20 in CLL and mantle cell lymphoma
CD7	T-lymphocytes, virtually all stages of development	T-cell lymphomas
		Characteristically lost in mycosis fungoides and adult T-cell leukemia/lymphoma syndrome
	B lymphocytes	Aberrant expression in CLL and AML
		Worse prognosis
CD8	T lymphocytes, late stages of development	T-cell lymphomas
		Characteristically reduced or negative in most mycosis fungoides
		$CD30^+$ lymphoproliferative disorders
		Characteristically negative
	NK cells	Malignant NK cell neoplasms
		Negative in benign NK cell proliferations
	Some B lymphocytes	Aberrant expression in CLL
CD10	B lymphocytes	Precursor B-cell acute lymphoblastic leukemia
		Nodal follicular lymphoma
		Primary cutaneous follicular lymphoma
		Reduced or absent
		Burkitt lymphoma
		Primary cutaneous marginal zone lymphoma
		Negative
		Primary cutaneous large B-cell lymphoma of the leg
		Negative
		B-cell pseudolymphomas
		CLL
		Worse prognosis
CD15	Reed-Sternberg cells	Classic Hodgkin lymphoma
	Lymphocyte-predominant cells	Nodular lymphocyte-predominant Hodgkin lymphoma
		Negative
	T lymphocytes	$CD30^+$ lymphoproliferative disorders
		T-cell lymphomas
		Minority of mycosis fungoides are positive
CD19	B lymphocytes	Malignant B-cell neoplasms
		Benign B-cell proliferations
		Aberrant expression in plasma cell myelomas and AML

Table 1. Continued.

Immunostain	*Cells Identified*	*Used in*
CD20	B lymphocytes	Malignant B-cell neoplasms
		May be used to direct chemotherapy
		May be lost after treatment with anti-CD20 medication
		Benign B-cell proliferations
CD25	Activated B and T lymphocytes	Malignant neoplasms
		Used to direct chemotherapy
		Benign proliferations
	Mast cells	Aberrant expression in mastocytosis
CD30	Activated T lymphocytes	$CD30^+$ lymphoproliferative disorders
		Lymphomatoid papulosis type B tends to be negative
		Transformed mycosis fungoides
		Numerous benign disorders
		Molluscum contagiosum, Milker nodule, HSV or VZV, nodular scabies, etc.
	Reed-Sternberg cells	Classic Hodgkin lymphoma
CD34	Neutrophils	Myeloid leukemia cutis (6–17%)
CD38	Mature B lymphocytes	Plasma cell myeloma
		Not specific
		CLL
		Worse prognosis
		Lymphoplasmacytic lymphoma
CD56	NK cells	Nasal-type NK/T-cell lymphoma
		Blastic NK/T-cell lymphoma
		NK cell lymphoma/leukemia
		Early plasmacytoid dendritic cell leukemia/lymphoma
	T lymphocytes	$CD30^+$ lymphoproliferative disorders
		Cutaneous γδ T-cell lymphoma
		Rare in mycosis fungoides and cytotoxic peripheral T-cell lymphoma
	B lymphocytes	Plasma cell myeloma
		Higher incidence of bone lesions, overall better prognosis
NKI/C3 (CD63)	Activated basophils	Cellular neurothekeomas
		Hymenoptera venoma allergy
CD68	Macrophages/monocytes	Intravascular histiocytosis
		Desmoplastic cellular neurothekeoma
		Granulomatous or xanthogranulomatous disorders
	Malignant myeloid cells	Myeloid leukemia cutis
CD79a	B lymphocytes	B-cell neoplasms
		Plasma cell myelomas
	Malignant myeloid cells	Aberrant in AML and precursor T-cell lymphoblastic lymphomas
	T lymphocytes	
CD117	Malignant myeloid cells	AML
		CD117 inhibitors may be used for treatment
	Mast cells	Mast cell proliferations
		CD117 inhibitors may be used for treatment
	Merkel cells	Merkel cell carcinoma
		Does not respond to CD117 inhibitors
	T lymphocytes	$CD30^+$ lymphoproliferative disorders

Table 1. Continued.

Immunostain	*Cells Identified*	*Used in*
		May help differentiate between primary and secondary forms
		Systemic form strongly positive
		Mycosis fungoides
		Sézary syndrome
		Primary cutaneous pleomorphic T-cell lymphomas
CD138	Plasma cells	Plasma cell myeloma
		Solitary plasmacytomas
		Plasmablastic lymphoma
		Lymphoplasmacytic lymphoma
Bcl-2	B lymphocytes	Primary cutaneous marginal zone lymphoma
		Primary cutaneous follicular lymphoma
		Germinal centers usually negative
		Secondary cutaneous follicular lymphoma
		Benign B-cell proliferations
		Reactive germinal centers are negative
Bcl-6	B lymphocytes	Primary and secondary cutaneous follicular lymphoma
		Primary and secondary cutaneous marginal zone lymphoma
		Negative
		Angioimmunoblastic T-cell lymphoma
		Peripheral T-cell lymphoma NOS
		Negative
		DLBCL
		Primary cutaneous large cell lymphoma of the leg
Cyclin D_1	B lymphocytes	Mantle cell lymphoma
ALK	T lymphocytes	$CD30^+$ lymphoproliferative disorders
		Systemic form positive in 50–80% of cases
		ALK-positive systemic ALCL has 90% 5-year survival
		DLBCL
		Aggressive, responds poorly to chemotherapy
TdT	Immature B and T lymphocytes	Precursor B- and T-cell acute lymphoblastic leukemia/lymphoma
		Lymphoblastic lymphoma
	Merkel cells	Merkel cell carcinoma
	Myeloid blasts	AML
MUM1	B lymphocytes	Intravascular lymphoma
		Plasma cell myeloma
		Worse prognosis
		Classic Hodgkin lymphoma
		Better prognosis
		DLBCL
		Worse prognosis
		Primary cutaneous large B-cell lymphoma, leg type
		$CD30^+$ lymphoproliferative disorders
		T-cell lymphomas
		Mostly negative
MITF	Melanocytes	Benign nevi
		Melanoma
	Mast cells	Mast cell leukemia
		Cutaneous mastocytomas
		Cellular neurothekeoma

Table 1. Continued.

Immunostain	*Cells Identified*	*Used in*
Myeloperoxidase	Neutrophils	Leukemia cutis (40–60%)
Lysozyme	Neutrophils	Leukemia cutis
		Histiocytic sarcoma

ALCL = anaplastic large cell lymphoma; ALL = acute lymphoblastic leukemia; AML = acute myelogenous (myeloid) leukemia; CLL = chronic lymphocytic leukemia; DLBCL = diffuse large B-cell lymphoma; HSV = herpes simplex virus; NK = natural killer; NOS = not otherwise specified; VZV = varicella-zoster virus.

CD5

CD5 is a protein expressed on the surfaces of maturing T cells and some B cells (see Figure 2). It is expressed in both mature and malignant T cells. It is not specific for any T-cell malignancy, although its expression can be lost in T-cell lymphomas.[1] CD5 is primarily used to rule out the diagnoses of chronic lymphocytic leukemia and mantle cell lymphoma. Both of these neoplasms coexpress B-cell markers such as CD20 with CD5 (Figure 4).[26,27]

CD7

CD7 is a transmembrane protein of the immunoglobulin superfamily. CD7 is found on T cells at all levels of maturation (see Figure 2).[1,28] Given that CD7 is present in all T cells, it is readily demonstrated in both normal T cells and T-cell neoplasms. Aberrant loss of CD7 expression is seen in several T-cell lymphomas, characteristically MF and adult T-cell leukemia/lymphoma syndrome (see Figure 3).[1,14,29] Aberrant positive expression has been demonstrated in rare cases of chronic lymphocytic leukemia and acute myelogenous leukemia, where it portends a worse prognosis.[25,30]

CD8

CD8 is a glycoprotein that, similar to CD4, begins to be expressed in the later stages of T-cell development (see Figure 2). CD8-positive T cells are also termed cytotoxic or suppressor T cells.[1,16] CD8 also functions as part of the T-cell receptor, however, and is specific for class I major histocompatibility proteins.[31] It is expressed in both benign and malignant T cells, similar to CD4. Whereas CD4 is positive in most T-cell lymphomas, CD8 is almost always markedly reduced or absent, although rare cases of MF may express CD8 strongly (see Figure 3).[13,18,19] The CD30-positive lymphoproliferative disorders also usually stain negatively for CD8.[13,18,19,21] As discussed above, SPTL stains predominantly CD8 positive.[22,23] Natural killer cell leukemias also frequently express CD8, unlike benign natural killer cell proliferations, which stain CD4 positive.[1] CD8 may also be aberrantly expressed in chronic lymphocytic leukemia, although this has no known prognostic significance.[1,32]

CD10

CD10, also referred to as the common acute lymphoblastic leukemia antigen (CALLA), is a frequently used

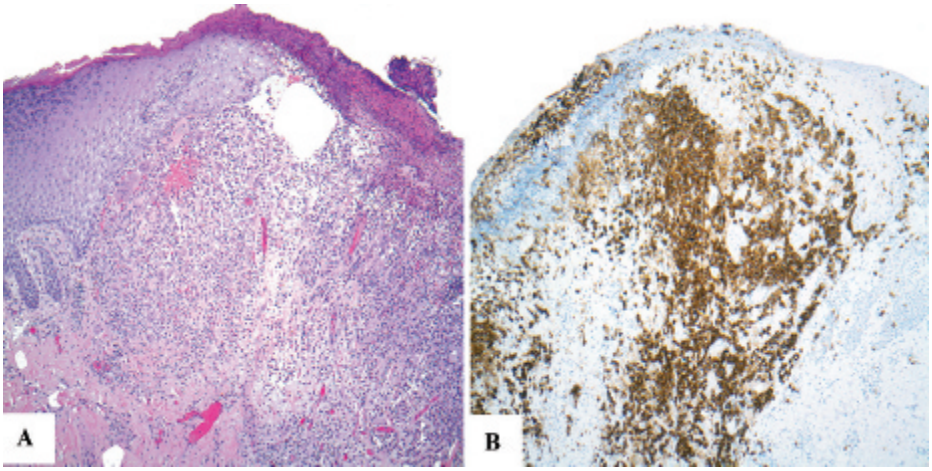

Figure 1. *A*, This patient has Langerhans cell histiocytosis, and a biopsy shows a proliferation of Langerhans cells with admixed eosinophils with a background of edema and ulceration (hematoxylin-eosin stain; ×200 original magnification). *B*, The Langerhans cells were positive for CD1a (CD1a immunostain; ×200 original magnification).

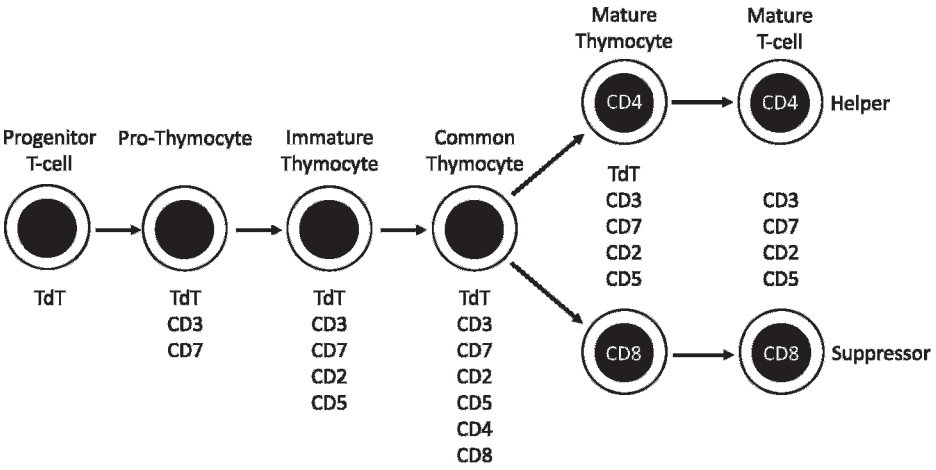

Figure 2. T-lymphocyte differentiation and the markers expressed during each stage.

B-cell marker that is expressed by almost all cases of precursor B-cell acute lymphoblastic leukemia (see Figure 4).[1] CD10 coexpression with CD19 or CD20 is seen in nearly all cases of nodal follicular lymphoma and Burkitt lymphoma.[33] Some authors have described slightly decreased CD10 expression in primary cutaneous follicular lymphoma[34]; however, other authors contend that CD10 expression is markedly reduced in these cases.[35,36] The neoplastic cells of primary cutaneous marginal zone lymphoma and primary cutaneous large B-cell lymphoma

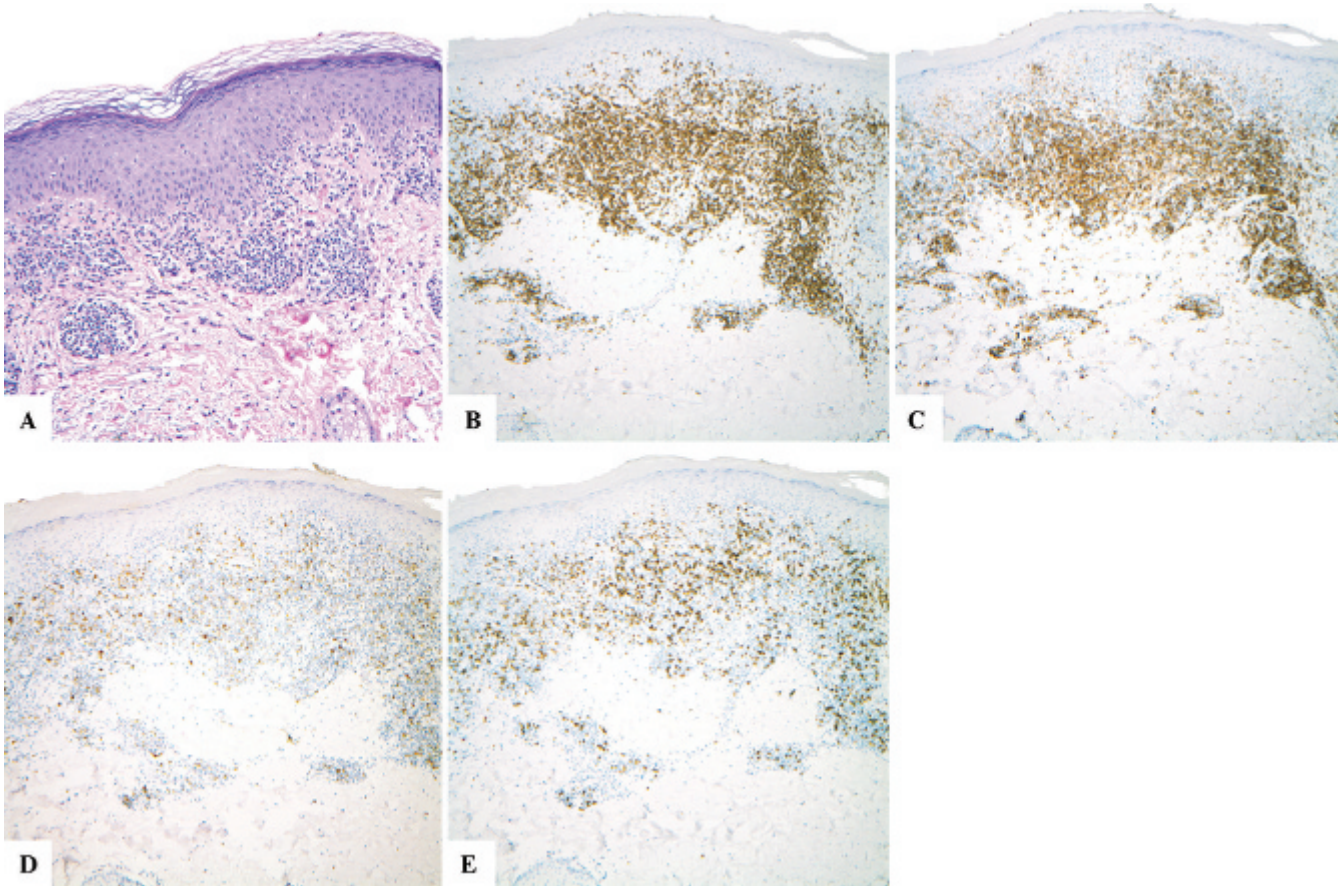

Figure 3. *A*, This case of mycosis fungoides has a patchy, superficial, lichenoid infiltrate of atypical lymphocytes with epidermotropism (hematoxylin-eosin stain; ×200 original magnification). The lymphocytes are positive for (B) CD3 and (C) CD4 with a marked loss of (D) CD7 and (E) CD8 (CD3, CD4, CD7, and CD8 immunostains, respectively; ×200 original magnification).

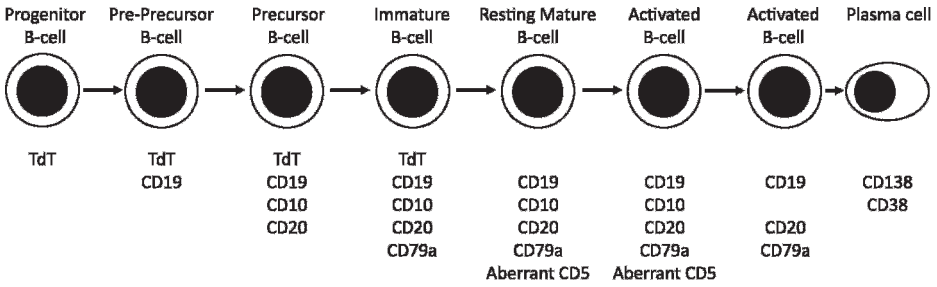

Figure 4. B-lymphocyte differentiation and the markers expressed during each stage.

of the leg stain consistently negative, although the surrounding dendritic network may stain positively. B-cell pseudolymphomas typically stain positive with CD10 in the germinal centers, similar to reactive lymph nodes, although the staining may vary in intensity. CD10 also will have a reticular staining pattern surrounding follicular and epithelial structures. These cells may also coexpress CD20 because germinal centers are composed of B cells. Thus, CD10 is perhaps best when coupled with bcl-2 and bcl-6 immunostains as the pattern of positivity seen with the combination of these three markers has been reported to be consistent enough for diagnosis.[36] When CD10 is aberrantly expressed in chronic lymphocytic leukemia, it heralds a worse prognosis.[37]

CD15

CD15 is a carbohydrate adhesion molecule that mediates phagocytosis and chemotaxis on normal neutrophils, macrophages, and tissue histiocytes.[1,38]

CD15 expression is most relevant to dermatologists in cutaneous CD30-positive lymphoproliferative disorders and Hodgkin lymphoma. A recent study showed that 43% of anaplastic large cell lymphoma (ALCL), 18% of LyP, and 9% of MF demonstrated CD15 positivity.[39] Rarely, Hodgkin lymphoma can metastasize to the skin, and when examined histologically, the scattered large, atypical cells of nodular lymphocyte-predominant Hodgkin lymphoma, called "lymphocyte-predominant cells" (also referred to as popcorn cells), stain CD15 negative. Lymphocyte-predominant cells are not Reed-Sternberg cells[40] as Reed-Sternberg cells are found only in the four variants of classic Hodgkin lymphoma. Reed-Sternberg cells stain CD15 positive in 75 to 85% of cases.[41] Because Reed-Sternberg cells represent a minor population in Hodgkin lymphoma proliferations and because many of them are bound by T cells, traditional flow cytometry rarely shows significant CD15 positivity. New methods have been developed that enable identification of Reed-Sternberg cells using flow cytometry in 89% of cases.[1,42]

CD19

CD19 is a protein receptor expressed on the surface of B cells (see Figure 4). Its expression is acquired at the earliest stage of B-cell development, maintained throughout maturation, and then lost in the plasma cell. CD19 is primarily measured by flow cytometry. Because it stains almost all stages of B cells, both benign and malignant B cells will mark positively. Thus, CD19 is used as a sensitive marker to identify the presence of B cells.[1] Plasma cell neoplasms and a small minority of acute myeloid leukemias may aberrantly express CD19, although no prognostic significance is associated with this aberrant expression.[43,44]

CD20

CD20 is a transmembrane protein expressed on the surface of B cells beginning in the pre-precursor B cell, and its expression is maintained until the plasma cell stage of maturation (see Figure 4).[1] Hence, all mature B cells, whether benign or malignant, generally strongly express CD20. One exception is that of chronic lymphocytic leukemia, in which the neoplastic cells may have only a dim expression of CD20 by flow cytometry.[45] CD20 may be aberrantly expressed in plasma cell myeloma and rare T-cell lymphomas.[46,47]

With the advent of anti-CD20 chemotherapeutic agents such as rituximab, CD20 positivity is now used to direct chemotherapeutic regimens.[48] After using anti-CD20 chemotherapy, the immunophenotypic and morphologic profile of the malignant cells may change. In one recent study, 27% of cases showed loss of CD20 by the neoplastic cells. Several of the cases also demonstrated either proliferation of plasmacytoid cells, transformation to classic Hodgkin lymphoma, or transformation to ALCL-like undifferentiated lymphoma after anti-CD20 treatment.[49]

CD23

CD23 is a low-affinity receptor for IgE that occurs in two isoforms, a and b. CD23a is found only on activated B

cells, and resting mature B cells and maturing B cells will not express this. CD23b is expressed on various hematopoietic cells.[1,50]

CD23 is a marker used primarily in flow cytometry. It has utility in helping differentiate between chronic lymphocytic leukemia (typically positive) and mantle cell lymphoma (typically negative or very weakly expressed) with flow cytometry.[51] Follicular lymphoma may also express CD23, but the phenotypic identity of follicular lymphoma (CD20 and CD10 positive) is different from that of chronic lymphocytic leukemia (CD20 and CD5 positive).[52] CD23 can also be used to identify the network of dendritic cells within lymphoid neoplasms similar to CD21.[53]

CD25

CD25 is the alpha chain of the interleukin-2 receptor found on activated T and B cells. Given that CD25 is present on the surface of activated T and B cells, it is present in inflammatory, autoimmune, and malignant lymphoid conditions. In lymphoid malignancies, it is used to direct chemotherapeutic regimens, not for diagnosis. Aberrant expression of CD25 by mast cells has also been identified as a diagnostic marker of mastocytosis when measured by flow cytometry.[54]

CD25 positivity indicates susceptibility to anti-CD25 chemotherapeutic regimens. The presence of this protein is particularly important when neoplasms are refractory to other forms of treatment. The Food and Drug Administration has approved treatment of some T- and B-cell malignancies with anti-CD25 agents, including cutaneous T-cell lymphoma/MF.[55–57] Anti-CD25 medications are also routinely used for treating graft-versus-host disease and preventing transplant rejection and are being investigated in a variety of inflammatory conditions, including psoriasis and inflammatory bowel disease.[58–61]

CD30

CD30 is a receptor belonging to the tumor necrosis factor family of proteins.[62] It is expressed by activated B and T cells and activated macrophages.[1]

Although CD30 can be positive in up to one-third of B- and T-cell non-Hodgkin lymphomas, it is most characteristically associated with LyP, ALCL, and Hodgkin lymphoma. CD30 positivity is the common defining feature of LyP and ALCL (Figure 5). Type A and Type C LyP specimens stain positively in 100% of cases. Type B specimens tend to be negative.[10,63] CD30 also stains the Reed-Sternberg cells in virtually 100% of classic Hodgkin lymphoma and is more sensitive for these cells than CD15.[41]

Less than 25% of patients with MF will undergo transformation, where the malignant cells become larger and more numerous, the tumor extent becomes more diffuse, epidermotropism is decreased, and the clinical course is much more aggressive. CD30 has been shown to be positive in approximately 50% of these transformations, and strong expression of CD30 in the transformed cells has been associated with an improved prognosis (Figure 6).[64–66]

CD30 may also be positive in benign lymphoid infiltrates of the skin, including the Milker nodule, herpes simplex virus or varicella-zoster virus infections, lymphomatoid drug reaction, molluscum contagiosum, nodular scabies, cutaneous leishmaniasis, syphilis, and pernio, among others. Not only will occasional large, atypical cells stain positively, but clusters of CD30-positive cells may also be identified, and some may exhibit a positively staining perinuclear dot in the region of the Golgi apparatus, mimicking CD30-positive malignant lymphomas.[67]

CD34

CD34 is a transmembrane sialomucin protein that is expressed on hematopoietic blasts and vascular tissue. It is believed to be involved in cell-to-cell signaling, although its exact function is uncertain.[68] Despite being expressed on early benign hematopoietic precursors, CD34 is positive in only 6 to 17% of granulocytic leukemia cutis cases. CD34 is a specific, not sensitive, marker for leukemia cutis.[69–71] Histiocytic sarcomas are uniformly negative.[72]

CD38

CD38 is an integral membrane glycoprotein on the surface of mature B cells, plasma cells, natural killer cells, and T cells.[73] Pre-B and pre-T cells also express CD38. During the intermediate stages of maturation, CD38 expression is lost. When maturation is nearly complete, CD38 expression is regained.[1]

Because CD38 is not lineage specific, several lymphoid malignancies will show expression of CD38. Most characteristically, CD38 has been associated with plasma cell myeloma, although its expression is not specific for plasma cells.[74] It is also expressed in some chronic lymphocytic leukemias, and when it is expressed, it indicates an unfavorable prognosis.[75] It is also found in lymphoplasmacytic lymphoma, which is composed of an admixture of mature B and plasma cells.[76] CD38 positivity is seen in various other lymphoid malignancies that may

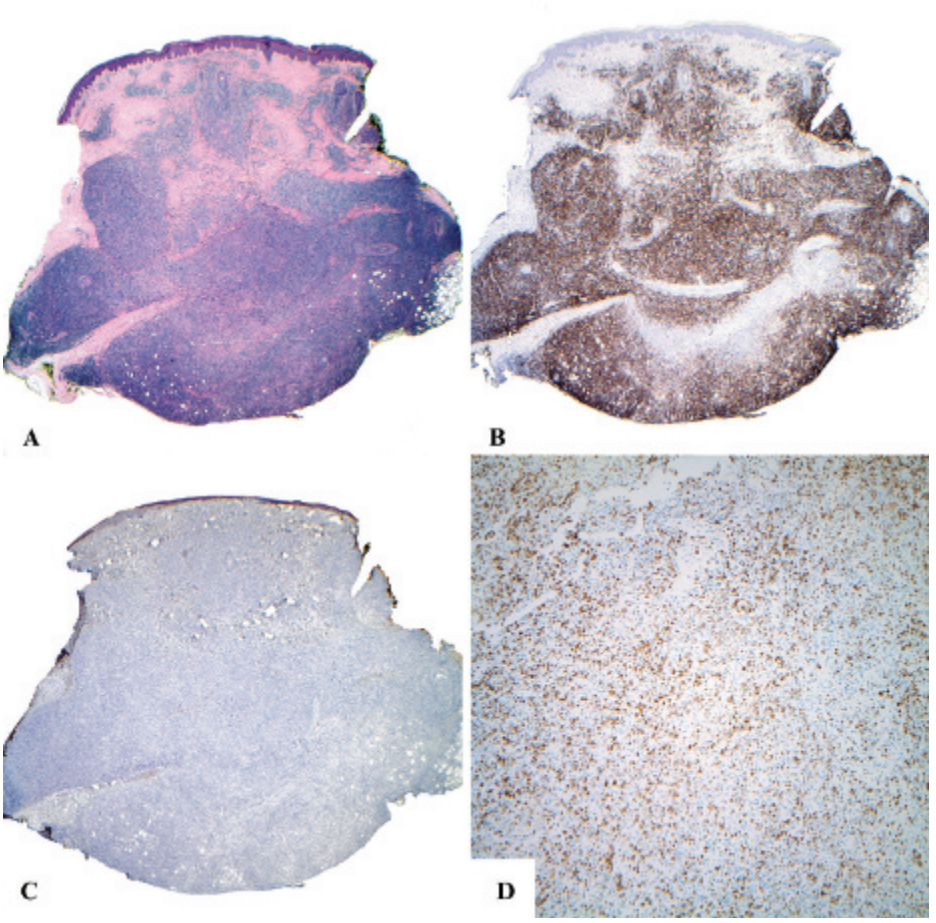

Figure 5. *A*, There is a superficial and deep dense diffuse infiltrate of atypical lymphocytes with an unremarkable epidermis (hematoxylin-eosin stain; ×200 original magnification). These lymphocytes are positive for (B) CD30 and negative for (C) ALK (CD30 and ALK immunostains, respectively; ×200 original magnification). When combined with morphology, this is diagnostic of primary cutaneous anaplastic large cell lymphoma. *D*, The primary systemic form of this disease is positive for ALK (ALK immunostain; ×200 original magnification).

involve the skin, but no prognostic significance is attached to its expression.[1]

CD56

CD56, also known as neuronal cell adhesion molecule (NCAM), is involved in cell-to-cell adhesion. It is expressed in all natural killer cells, a very small minority of T cells, and malignant plasma cells.[1]

CD56 is routinely expressed in nasal-type NK/T-cell lymphomas, blastic NK/T-cell lymphoma, NK cell lymphoma/leukemia, and early plasmacytoid dendritic cell leukemia/lymphoma.[77–79] Rare cases of CD56-positive MF and cytotoxic peripheral T-cell lymphoma have also been

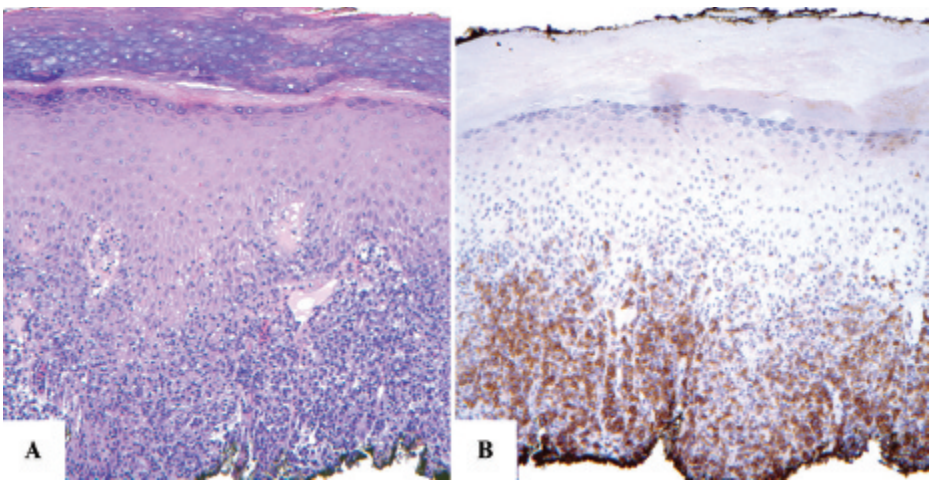

Figure 6. *A*, Similar to the other case of mycosis fungoides, this patient has a lichenoid infiltrate of atypical lymphocytes with epidermotropism (hematoxylin-eosin stain; ×200 original magnification). *B*, However, the lymphocytes are much larger and positive for CD30, signaling the large cell transformation of mycosis fungoides (CD30 immunostain; ×200 original magnification).

reported.[80,81] Although most CD56-positive cutaneous lymphomas have an overall poor prognosis, CD30-positive cutaneous ALCL maintains a good prognosis even with CD56 positivity.[82] As mentioned previously, malignant plasma cells may also express CD56. When part of multiple myeloma, CD56 positivity indicates a higher incidence of lytic bone lesions and an overall better prognosis than CD56-negative myeloma.[83]

SPTL was recently redefined by the World Health Organization–European Organization for Research and Treatment of Cancer to express only α and β receptors of the T lymphocyte. These lymphomas are CD4 negative, CD8 positive, and CD56 negative. They behave indolently when not accompanied by hemophagocytic syndrome. This newly redefined SPTL has an overall 5-year survival rate of 82% (46% if hemophagocytic syndrome is present, 91% if without). The previously described γδ variants of SPTL have been recategorized as cutaneous γδ T-cell lymphomas, a provisional World Health Organization diagnostic category. These malignancies are generally CD4 negative, CD8 negative, and CD56 positive. Skin ulceration, invasion of the superficial dermis, and hemophagocytic syndrome are more common. They have a worse response to therapy and behave more aggressively. Five-year survival is approximately 10% for this phenotype.[84]

NKI/C3 (CD63)

NKI/C3 is a monoclonal antibody directed against the melanoma-associated antigen, a glycoprotein originally described in the cytoplasm and vacuoles of cells with abundant melanosomes. It has since been reported to be positive in fibrohistiocytic tumors, granular cell tumors, juvenile xanthogranulomas, atypical fibroxanthomas, and cellular neurothekeomas, among others, but, paradoxically, has not shown utility in the diagnosis of melanoma.[85] Demetrick and colleagues reported that NKI/C3 is identical to CD63, a lysosomal protein found in basophils and mast cells.[86]

NKI/C3 can be measured via immunohistochemistry, flow cytometry, and real-time reverse transcriptase–polymerase chain reaction (RT-PCR). Most recently, it has been touted as a useful marker in the diagnosis of cellular neurothekeoma, and in one study, 9 of 11 cellular neurothekeomas stained positively with NKI/C3 and microphthalmia transcription factor (MITF). S-100 protein, which stains positively in typical myxoid neurothekeomas, was shown not to be expressed in 11 of 11 cellular neurothekeomas in one study.[87] Recently, some authors disputed the usefulness of NKI/C3, arguing that positive staining in such a broad spectrum of neoplasms renders interpretation of NKI/C3-positive staining in cellular neurothekeomas nonspecific at best. These authors emphasized that morphology coupled with immunohistochemistry is more specific than relying on immunohistochemistry alone.[21] Quantitative RT-PCR has been used to elucidate the various genetic mutations found in melanoma, and *NKI/C3* was one of the three most commonly mutated genes.[88]

When measured via flow cytometry, NKI/C3 is used in performing the basophil activation test.[89,90] This test, which is rarely used in dermatology, is useful in diagnosing allergy to *Hymenoptera* venom, although it has also shown utility in evaluating other allergies.[89,90] Although individuals with *Hymenoptera* allergy have elevated IgE levels, measurement of NKI/C3 levels is also useful as they are elevated only after there has been crosslinking of IgE receptors on basophils, which activates them and is a more specific finding than elevated IgE levels alone, which may be elevated even when there is monovalent binding of IgE receptors on basophils and then classified as nonactivated basophils.[89] NKI/C3 is also elevated in the mast cells found in mastocytosis and the basophils in chronic urticaria.[54,91]

CD68

CD68 is a glycoprotein present on the surface of macrophages/monocytes, which binds to low-density lipoprotein. It stains both benign and malignant macrophages/monocytes.[92] CD68 positivity is seen in benign disorders such as intravascular histiocytosis, desmoplastic cellular neurothekeomas, and other granulomatous/xanthogranulomatous conditions.[93–96] CD68 expression in malignancies has also been reported, with positivity noted in myeloid leukemia cutis as high as 94%.[97] Langerhans cell histiocytosis does not stain positively for CD68 despite the word "histiocyte" in the diagnosis.[96]

CD79a

CD79 is a multimeric complex composed of two parts, CD79a and CD79b. CD79a expression begins in the precursor B-cell stage and is lost in the early plasma cell (see Figure 4). Thus, virtually all B-cell neoplasms will stain with CD79a.[1] In contrast, only 50% of plasma cell neoplasms stain positively.[98] A rare subset of acute myeloid leukemias and precursor T-cell lymphoblastic lymphomas will stain positively.[99]

CD117

CD117, or c-kit, is the stem cell receptor ligand and can be found on benign immature myeloid cells.[1] Given that imatinib mesylate is one of a few CD117 inhibitors, CD117 is primarily used to direct treatment of neoplasms that express CD117, many of which are cutaneous.[100]

Noncutaneous neoplasms such as gastrointestinal stromal tumors stain positively for CD117 and typically respond to CD117 inhibitors such as imatinib.[101] The response to treatment of cutaneous neoplasms has been less promising, however. Acute myeloid leukemias and mast cell disorders stain positively with CD117,[100,102–104] and some CD117 inhibitors have shown promise in treating acute myeloid leukemia and mastocytosis.[105] However, imatinib has shown minimal efficacy in treating acute myeloid leukemia.[100,104] Imatinib also performed suboptimally in patients with systemic mastocytosis. Although 50% of aggressive systemic mastocytosis patients responded to imatinib treatment, the response to treatment in those with indolent systemic mastocytosis and systemic mastocytosis with clonal hematologic non–mast cell lineage disease was 14% and 9%, respectively.[103] Merkel cell carcinomas also stain strongly positive with CD117, which has prompted a clinical trial with imatinib. Unfortunately, patients rapidly progressed even with imatinib treatment, and the trial was closed.[106] Thus, CD117 expression does not necessarily indicate that the process will respond to treatments directed at this marker.

Systemic CD30-positive ALCL and Hodgkin lymphoma have also demonstrated CD117 expression. Investigations into primary cutaneous CD30-positive ALCL, MF, primary cutaneous pleomorphic T-cell lymphoma, and Sézary syndrome found weak CD117 positivity in a small percentage of malignant cells in 20 to 40% of cases. CD117 may have utility in differentiating between systemic and primary cutaneous forms of CD30-positive ALCL as the systemic form is generally strongly CD117 positive.[107]

CD138

CD138, also known as syndecan-1, is a transmembrane heparan sulfate proteoglycan expressed only in plasma cells containing cytoplasmic immunoglobulin.[108] Given its specificity, CD138 expression is routinely seen in plasma cell myeloma, plasmacytomas (Figure 7), plasmablastic lymphoma, and lymphoplasmacytic lymphoma, although CD138 is also expressed in benign plasma cells.[1,76] Of note, flow cytometry is a poor method of quantifying plasma cells using CD138. The cells are relatively fragile, and, as a result, the cytoplasm is easily stripped away in the technique. The cells are also large, which may cause them to fall outside the gates used in flow cytometry to analyze cell populations.[1]

Bcl-2

Bcl-2 is a proto-oncogene that blocks apoptosis.[109] It is localized to internal cell membranes, including the nuclear envelope, endoplasmic reticulum, and outer mitochondrial membrane.[110] It is expressed by the majority of mature B and T cells; thus, numerous benign and malignant B- and T-cell conditions will express Bcl-2.[1]

Staining for Bcl-2 is primarily used in hematopathology to distinguish follicular lymphoma from benign reactive lymphoid infiltrates. It is also useful in distinguishing

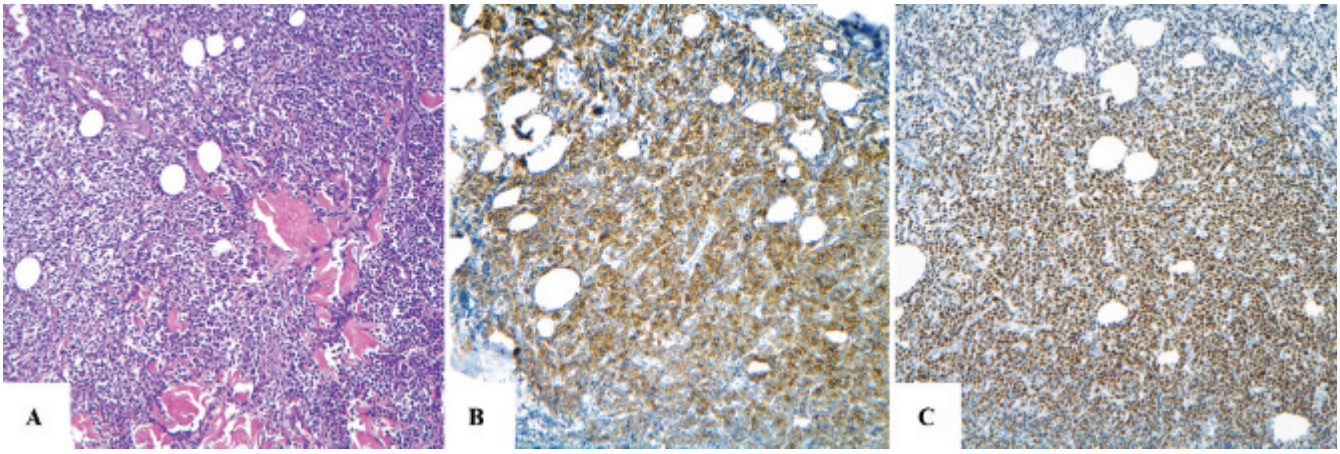

Figure 7. *A*, The dermis has a deep dermal and subcutaneous infiltrate of atypical cells that are positive for (B) CD138 and (C) MUM1, confirming a cutaneous plasmacytoma (hematoxylin-eosin, CD138, and MUM1 immunostains, respectively; ×200 original magnification).

between primary and secondary cutaneous follicular lymphoma as well as primary cutaneous marginal zone lymphoma. Reactive germinal centers will not stain positively with Bcl-2, although primary cutaneous marginal zone lymphoma and the neoplastic germinal centers seen in secondary cutaneous follicular lymphoma will routinely stain positively with Bcl-2. However, primary cutaneous follicular lymphoma generally stains negatively for Bcl-2. This is not universal, however, as Bcl-2 expression in follicular lymphoma also varies inversely with the histologic grade and Ki-67 proliferation index.[35,111,112]

Bcl-6

Bcl-6 is a zinc finger protein that represses deoxyribonucleic acid (DNA)-binding transcription. It is expressed in germinal center B cells and is a hallmark of benign cells that have been through germinal center maturation. Rare T cells can also express Bcl-6.[113]

Bcl-6 is useful in differentiating between follicular lymphoma and marginal zone lymphoma when histology or other immunophenotypic markers are inconclusive. Generally speaking, both primary and secondary cutaneous follicular lymphoma stain positively for Bcl-6. Primary and secondary cutaneous marginal zone lymphoma, in contrast, stain negatively for Bcl-6.[35,114,115] It is also useful to differentiate between angioimmunoblastic T-cell lymphoma and peripheral T-cell lymphoma that is not otherwise specified (NOS). Angioimmunoblastic T-cell lymphoma stains predominantly Bcl-6 positive, whereas peripheral T-cell lymphoma NOS generally stains Bcl-6 negative.[116] Bcl-6 is also expressed in diffuse large B-cell lymphoma (DLBCL) and primary cutaneous large B-cell lymphoma of the leg.[35]

Cyclin D_1

Cyclin D_1 is one of many types of cyclins that comprise a family of proteins with significant control in regulating the cell cycle. Cyclin D_1 is critical in the progression of the cell cycle from G_1, when the cell can become senescent, to the S phase, where DNA divides in preparation for mitosis.[117]

Mantle cell lymphoma is the most frequent cutaneous malignancy for which cyclin D_1 is used for diagnosis. Morphologically, mantle cell lymphoma is extremely difficult to diagnose and can be indistinguishable from other lymphomas. In addition, it shares the basic phenotypic profile of other lymphomas. Cytogenetics can identify the characteristic t(11;14)(q13;q32) translocation seen in most mantle cell lymphomas. However, the only immunohistochemical stain that reliably identifies mantle cell lymphoma from other lymphomas is cyclin D_1.[26,118]

ALK

Anaplastic lymphoma kinase (ALK) is an immunohistochemical stain that detects ALK protein expression as part of the NPM-ALK fusion protein. The NPM-ALK fusion protein is the result of a translocation between the *ALK* gene on chromosome 2 and the nucleophosmin gene on chromosome 5.[119]

ALK is primarily useful in ALCL. Systemic ALCL is ALK positive in 50 to 80% of cases (see Figure 5).[120] The 5-year survival rate of systemic ALCL is related to ALK expression. Patients who have ALK-positive systemic tumors have a 5-year survival rate around 90%; however, those with ALK-negative systemic tumors have a 5-year survival rate of only 30 to 40%.[121] Primary cutaneous ALCL is almost universally ALK negative, although very rare cases of ALK-positive primary cutaneous ALCL have been described (see Figure 3).[122] Thus, ALK may be helpful in determining whether a cutaneous ALCL is primary cutaneous or secondary with cutaneous involvement, but it is not 100% accurate. Definitive determination of the primary site depends on clinical staging in correlation with pathologic and radiologic findings.[123] ALK is also positive in a variant of DLBCL. ALK-DLBCL has plasmablastic differentiation, tends to be aggressive, and responds poorly to chemotherapy.[124]

TdT

TdT stands for terminal deoxynucleotidyl transferase and is an intranuclear DNA polymerase responsible for adding N-nucleotides and joining exons during immunoglobulin gene rearrangement.[1,125] It is a marker of immaturity and, as such, is expressed by immature B and T cells, as well as some myeloid blasts (Figure 8). When precursor B- and precursor T-cell lymphoblastic leukemias/lymphomas and some subtypes of acute myeloid leukemia involve the skin, TdT may be used for diagnosis.[126,127] TdT is also positive in 73% of Merkel cell carcinomas. Morphologically, Merkel cell carcinoma can be similar to lymphoblastic lymphoma, which is also TdT positive. Further diagnostic pitfalls may arise because both Merkel cell carcinoma and lymphoblastic lymphoma may stain negatively for CD45 and CD20 yet express other B-cell markers.[128]

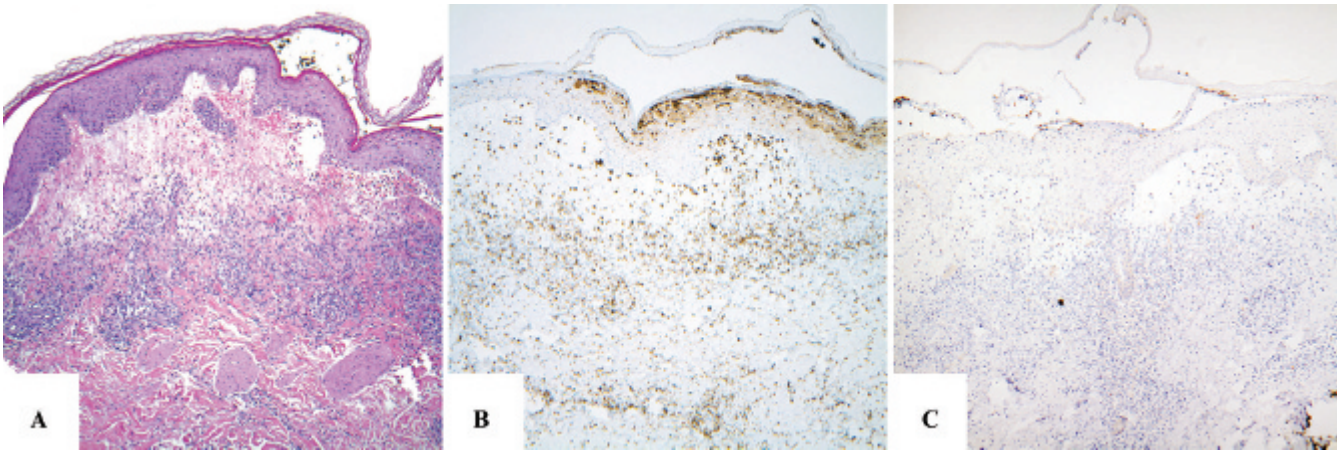

Figure 8. *A*, A patient with acute myeloid leukemia has a new onset of papules that have marked papillary dermal edema and an infiltrate of atypical cells in the superficial dermis (hematoxylin-eosin stain; ×200 original magnification). *B*, Myeloperoxidase staining confirms that the infiltrate is granulocytic, diagnostic of leukemia cutis (×200 original magnification). *C*, These myeloid blasts were negative for TdT (TdT immunostain; ×200 original magnification).

MUM1

MUM1, the multiple myeloma oncogene-1, is expressed in late germinal center or post–germinal center B cells.[129,130] A recent study investigated MUM1 expression in intravascular lymphoma, a subtype of DLBCL. All 12 cases were found to stain positively for MUM1, including 8 cases in the skin.[131] Given that MUM1 is expressed in plasma cells, many plasma cell myelomas will be positive (see Figure 7). Expression of MUM1 indicates a worse prognosis for these patients.[130]

MUM1 is also expressed in approximately 92% of classic Hodgkin lymphoma. The cases lacking MUM1 expression had shorter time to progression and decreased overall survival.[132] MUM1 is also positive in 40 to 50% of DLBCLs. Whereas MUM1 expression portends a better prognosis in classic Hodgkin lymphoma, MUM1 expression in DLBCL is associated with a poor prognosis.[133,134] MUM1 is also expressed in 80 to 100% of cutaneous CD30-positive lymphoproliferative disorders and in only a minority of other peripheral T-cell lymphomas.[135,136] One-third of mantle cell lymphomas also stain MUM1 positive.[129]

MUM1 is important in differentiating between the two types of primary cutaneous DLBCL: follicle center lymphoma and large B-cell lymphoma, leg type. When compared to the leg type of large B-cell lymphoma, follicle center lymphomas have a significantly improved 5-year overall (92% to 53%) and disease-free (100% to 68%) survival. MUM1 has been shown to be expressed in approximately 90% of large B-cell lymphoma, leg-type tumors, and 10% or less of follicle center lymphomas.[134,137] Thus, MUM1 is a reliable adjunct to accurately distinguishing between these two morphologically similar yet prognostically different lymphoma subtypes.

MITF

MITF, which stands for microphthalmia transcription factor, is a transcription factor integrally involved in melanocyte development. It is an oncogene expressed in some melanomas and has been reported to have a sensitivity of 81 to 100% and a specificity of 88 to 100%. These rates are lower in lesions with a spindle cell morphology, however.[138] Benign melanocytic nevi also express MITF.[139] Recently, MITF has been shown to be useful in diagnosing cellular neurothekeomas as 81% express it.[87] Angiomyolipomas of the liver and kidney also stain positively, although this has not been evaluated in cutaneous angiomyolipomas.[140] Mast cells also stain positively, which can be useful in differentiating cutaneous mastocytomas and mast cell leukemia from myeloid leukemia cutis.[141]

Myeloperoxidase and Lysozyme

Myeloperoxidase and lysozyme are enzymes found in abundance within the cytoplasmic granules of neutrophils.[142,143] Antibodies directed against these enzymes are useful in identifying cells of granulocyte lineage, particularly with leukemia cutis. Forty to 60% and nearly 100% of leukemia cutis cases are positive with myeloperoxidase (see Figure 8) and lysozyme immunostains, respectively.[69,70] This does not necessarily correlate with flow cytometry,

which identifies myeloperoxidase expression in a greater percentage of cases.[70] Eighty-six percent of histiocytic sarcomas are positive for lysozyme but are uniformly negative for myeloperoxidase.[71]

Conclusions

Over the last number of years, there has been a virtual explosion in the number of antibodies that have been developed and commercialized that are now being used diagnostically and even therapeutically for many different diseases, a number of which affect the skin either primarily or secondarily. It is important that dermatologists have at least a general understanding of some of the ones that are more commonly employed and how to interpret results when they are reported in pathology reports as this may influence diagnosis and therapy.

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