Approach to dermal-based lymphoid infiltrates and proliferations

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Abstract

The histopathological diagnosis of dermal-based lymphoid infiltrates and proliferations is often challenging due to the vast list of biologically diverse entities that archetypally or occasionally center in the mid-dermis, especially because significant overlap exists in their clinical, histopathologic, and immunophenotypic features. The differential diagnosis includes reactive infiltrates in common and rare inflammatory dermatoses, benign conditions that may mimic lymphoid neoplasms (pseudolymphomas), and true clonal proliferations arising either primarily in the skin or rarely in extracutaneous tissues with secondary cutaneous dissemination. While numerous histopathological and immunophenotypic features have been reported to support a definitive diagnosis, no single ancillary test is sufficient for their distinction. Therefore, in this review we advocate a stepped histopathological approach for dermal-based lymphoid infiltrations, employing as key elements the general lymphocytic composition (relative B- versus T-cell ratio), coupled with the predominant cytomorphology (cell size) present. Following this strategy, the relative incidence of cutaneous involvement by each disease should always be considered, as well as the notion that a definitive diagnosis must be founded on a multiparameter approach integrating all clinical, histopathologic, immunophenotypic, and—in selected cases—molecular features.

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Cutaneous lymphoid infiltrates and proliferations centered upon the dermis are common in dermatopathology/surgical pathology, especially those pertaining to inflammatory dermatoses.[1] Less commonly, these represent true clonal neoplasms with a myriad of proliferations, most frequently arising in the skin without evidence of extracutaneous disease (primary cutaneous [PC] lymphomas [PC-Ls] and lymphoproliferative disorders [PC-LPDs]) and rarely secondarily, following dissemination from nodal or extranodal (EN) tissues (secondary cutaneous [SC] lymphomas [SC-Ls]).[2,3] The 2016 revision to the World Health Organization (WHO) classification of lymphoid neoplasms (2016 WHO revision) includes 70 distinct entities within neoplasms of mature B- and T-/natural killer (NK) cells, Hodgkin lymphoma (HL), and posttransplant lymphoproliferative disorders; amongst these, 11 are primary cutaneous, although in many more (>15) the skin may seldom be the primary site of involvement or more commonly be affected secondarily during disease progression.[4]

The vast list of differential diagnoses posed by dermal-based cutaneous lymphoid infiltrates may overwhelm the pathologist because significant overlap exists amongst different entities and because no single ancillary test is sufficient for their distinction.[2,3] To simplify this conundrum, we suggest a practical histopathological approach to the differential diagnoses of cutaneous lymphoid infiltrates affecting preferentially the mid-dermis, excluding those centered upon the superficial dermis or subcutaneous fat. We conducted a literature review from 1966 to October 1, 2017, at PubMed.gov using the search terms "cutaneous lymphoma," "cutaneous pseudolymphoma," "cutaneous lymphoid hyperplasia," "simulants/mimics/imitators of cutaneous lymphomas," "cutaneous lymphoid infiltrates," and "cutaneous involvement by lymphoma," focusing our data compilation onto entities either archetypally or occasionally characterized by infiltrates or proliferations centered upon the dermis. To narrow down the differential diagnosis, we propose taking as a starting point the relative mixture of T and B cells observed and the predominant lymphocytic size present, constantly keeping in mind the relative incidence of dermal involvement by each disease. While this approach is intended to ease the challenge posed by dermal-based cutaneous lymphoid infiltrates, it is paramount to note that a final diagnosis will rely on thorough correlation of all clinical, histopathological, immunophenotypic, and—in selected cases—molecular features.[2,3] Other algorithmic approaches to cutaneous lymphoid infiltrates have been published by the International Society for Cutaneous Lymphomas,[5] the French National Cancer Institute,[6] and more recently, by one of us.[3]

Rationale for the suggested diagnostic approach

Histopathological discriminatory features reported in the differential diagnosis of dermal-based cutaneous lymphoid infiltrates are numerous and include a vast array of characteristics of the infiltrate, such as distribution within the tissue, epithelial accompanying changes, broad composition (purely lymphoid versus mixed with other inflammatory/microenvironment–related cells), predominant lymphocytic cytomorphology (small and monomorphous versus small to medium pleomorphic versus large atypical), and general immunophenotypic composition (B- versus T-cell predominance), as well as the detailed immunocategorization of lymphocytes (pre-B, pro-B,

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mantle B, marginal zone B, germinal center [GC] B "centrocytes and centroblasts," activated B "immunoblasts," plasma cells, plasmacytoid dendritic cells, T-helper, follicular T-helper, T-regulatory, T-cytotoxic, NK, pre-T, or precursor hematopoietic cells).[7-9] In addition to immunohistochemistry (IHC), in select cases, molecular techniques are required such as in situ hybridization (ISH) analysis of immunoglobulin light-chain (Igl) restriction (*kappa:lambda*) or Epstein-Barr virus–encoded RNA (EBER).[7-12] Likewise, immunoglobulin heavy-chain rearrangement analysis and T-cell receptor (TCR) clonality assessments by polymerase chain reaction (PCR) or next-generation sequencing, as well as fluorescent ISH for specific chromosomal translocations or aberrations, may be required.[13-16] The extensive list of features to discriminate different cutaneous lymphoid infiltrates adds to the inherent complexity of approaching such

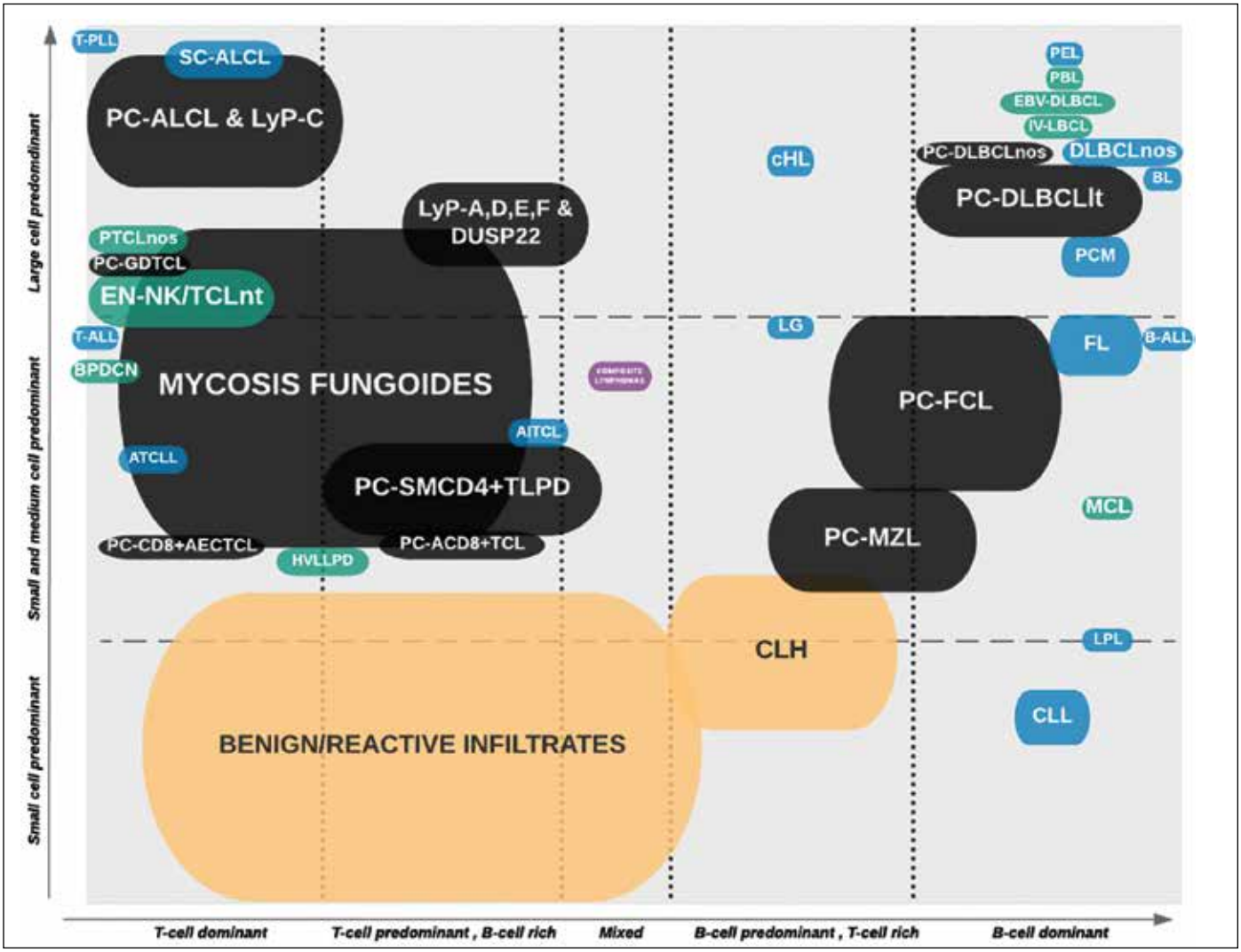

FIGURE 1. Dermal-based lymphoid infiltrates and proliferations subdivided by cell size (y-axis) and immunophenotypic predominance (x-axis). The size of the ovals reflects the relative frequency of cutaneous involvement by each disease. Oval colors indicate: **orange**, benign/reactive infiltrates; **black**, primary cutaneous lymphomas and LPDs; **green**, cutaneous lymphomas or LPDs either primary to the skin or systemic with secondary cutaneous involvement; **blue**, systemic lymphomas with secondary cutaneous involvement; and **purple**, composite lymphomas. ACD8+TCL, acral CD8+ T-cell lymphoma; AITCL, angioimmunoblastic T-cell lymphoma; ALCL, anaplastic large cell lymphoma; ALL, acute lymphoblastic leukemia/lymphoma; ATCLL, adult T-cell leukemia/lymphoma; B, B cell; BL, Burkitt's lymphoma; BPDCN, blastic plasmacytoid dendritic cell neoplasm; CD8+ AECTCL, CD8+ aggressive epidermotropic cytotoxic T-cell lymphoma; cHL, classic Hodgkin lymphoma; CLH, cutaneous lymphoid hyperplasia; CLL, chronic lymphocytic leukemia/small lymphocytic lymphoma; DLBCL, diffuse large B-cell lymphoma; EBV, Epstein-Barr virus; EN-NK/TCL, extranodal-natural killer/T-cell lymphoma; FCL, follicle center lymphoma; FL, follicular lymphoma; GDTCL, gamma/delta T-cell lymphoma; HVLLPD, hydroa vacciniforme-like LPD; IV-LBCL, intravascular large B-cell lymphoma; LG, lymphomatoid granulomatosis; LPD, lymphoproliferative disorder; LPL, lymphoplasmacytic lymphoma; lt, leg type; LyP, lymphomatoid papulosis; MCL, mantle cell lymphoma; MZL, marginal zone lymphoma; nos, not otherwise specified; nt, nasal type; PBL, plasmablastic lymphoma; PC, primary cutaneous; PCM, plasma cell myeloma; PEL, primary effusion lymphoma; PLL, prolymphocytic leukemia; PTCL, peripheral T-cell lymphoma; SC, secondary cutaneous; SMCD4+TLPD, small medium CD4+ T-cell lymphoproliferative disorder; T, T cell.

TABLE 1 Benign/reactive T-cell predominant dermal-based infiltrates

Disease	Typical clinical presentation	Major histopathological features	Typical immunophenotype
Benign/reactive T-cell predominant, perivascular superficial and deep (PSD), dermal-based infiltrates			
Drug & viral exanthems	~2-8 wks post-exposure (drugs); disseminated m-p rash	PSD ± vacuolar interface changes ± exocytosis ± spongiosis	↑ CD8:CD4
Pityriasis lichenoides	Self-limited (wks-yrs); scaly papules with collerette-like desquamation, ± ulceration; + on trunk & PE	Wedge-shaped PSD + vacuolar interface changes + exocytosis	↑ CD8:CD4 (PLEVA) ↑ CD4:CD8 (PL)
Actinic reticuloid	Chronic erythema & lichenification on sun-exposed sites	PSD + blurring of the DEJ + few apoptotic keratinocytes	↑ CD8:CD4
Gyrate erythemas	Erythematous curvilinear or annular macules ± scaling	Dense (coat sleeve-like) superficial or PSD	↑ CD4:CD8
Cutaneous lupus erythematosus	Annular erythematous & scaly or psoriasiform lesions (SCLE), erythematous edematous plaques (DLE & TLE) with atrophy and pigmentary change (DLE); + on sun-exposed sites	Periadnexal & PSD + interface changes, epidermal atrophy & BM thickening (in DLE, absent in TLE) + interstitial mucinosis	↑ CD4:CD8
Perniosis	Tender red-violaceous papules or nodules in association with cold exposure; + on acral surfaces.	Acral skin with a PSD infiltrate + subepidermal edema	CD3+; CD4:CD8 unknown
Polymorphic light eruption	Erythematous papules, patches, plaques or vesicles following sun exposure; on sun-exposed skin	Dense PSD + papillary dermal edema	↑ CD4:CD8 (early lesions) ↑ CD8:CD4 (late lesions)
Benign/reactive T-cell predominant, nodular to diffuse, dermal-based infiltrates			
Arthropod assaults	Intensely pruritic erythematous papules and/or nodules; commonly on genitalia, elbows and/or axillae	Wedge-shaped PSD to diffuse infiltrate + admixed histiocytes, eosinophils & few plasma cells	↑ CD4:CD8
Tattoo-ink related T-cell pseudolymphoma	Papules or nodules, mo-yrs after tattoo placement	Nodular-diffuse inf. + pigment between collagen or within histiocytes	↑ CD8:CD4
Idiopathic T-cell pseudolymphoma	Identical clinical, histopathological and immunophenotypic features as in primary cutaneous small medium CD4+ T-cell lymphoproliferative disorder; *see Table 2*		

Abbreviations: ~, approximately; ±, with or without"; ↑, elevated; BM, basement membrane; DEJ; dermal-epidermal junction; inf, infiltrate; mo, months; m-p; maculo-papular; PE, proximal extremities; PLC, pityriasis lichenoides chronica; PLEVA, pityriasis lichenoides et varioliformis acuta; PSD, perivascular superficial and deep infiltrate; wks, weeks; yrs, years.

a large differential diagnosis. Therefore, in our opinion, it is helpful (time and resource sparing) to follow a stepped approach, utilizing as starting points some of the most salient discriminatory features of cutaneous lymphoid infiltrates that allow an expedient narrowing down of differential diagnoses (ie, general lymphocytic composition and cytomorphology).[2,3] When following this approach, however, the pathologist should always consider the relative incidence of cutaneous involvement by each disease (Figure 1), and ultimately, clinicoimmunopathologic correlation remains the gold standard for diagnosis of all cutaneous lymphoid infiltrates.[2,3,7,8]

Diagnostic approach to dermal-based lymphoid infiltrates and proliferations relying on the predominant cytomorphology and immunophenotypic pattern

T-cell–dominant and T-cell–predominant dermal-based (reactive) infiltrates of small lymphocytes

T-cell–dominant or –predominant dermal-based infiltrates of small-sized monomorphic cells (excluding superficial perivascular or band-like infiltrates) typically display 2 main arrays of dermal distribution: as scant to dense superficial and deep perivascular infiltrates, or arrayed as nodular to diffuse aggregates (Table 1).[1] Sparse perivascular infiltrates include, in descending order of frequency, drug and viral exanthems (D/VEs), pityriasis lichenoides (PL), and more rarely, actinic reticuloid (AR). These typically show additional histopathological clues of their reactive nature, including limited spongiosis and/or basement membrane vacuolization (D/VE); epidermal changes (PL and AR); interface alteration (prominent in PL, variable in AR); erythrocyte extravasation (PL); and/or plasma cells, eosinophils, and/or multinucleated stellate myofibroblasts (AR).[1,3,17-19] When moderate to dense perivascular lymphocytic infiltrates dominate (Figure 2), the differential diagnosis is led by gyrate erythemas, cutaneous lupus erythematosus, perniosis, and polymorphic light eruption, all of which may also display accompanying epidermal and/or dermal clues for their differentiation but that are easily distinguished on clinical examination (see Table 1).[1,3,17-19] By contrast, dermal-based nodular to diffuse infiltrates composed mostly of small monomorphic T cells are rare

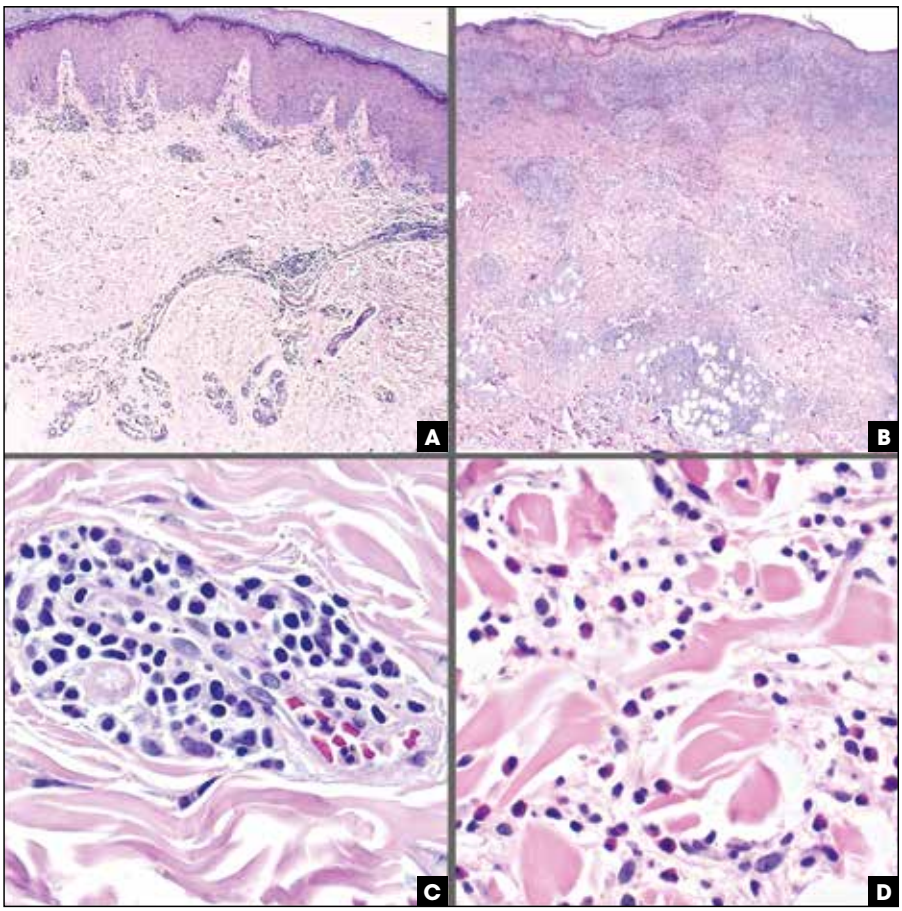

FIGURE 2. Examples of T-cell–dominant and T-cell–predominant B-cell–rich dermal-based (reactive) infiltrates of small lymphocytes. (A, C) Hematoxylin & eosin–stained slides, 40x and 200x, respectively; superficial and deep perivascular infiltrate of small lymphocytes on acral skin, in a patient with perniosis. **(B, D)** Hematoxylin & eosin–stained slides, 40x and 200x, respectively; nodular superficial and deep dermal-based infiltrate of small lymphocytes with admixed eosinophils and epidermal ulceration, in a patient with a persistent arthropod bite reaction.

and typically represent benign dermatoses categorized under the umbrella term of T-cell pseudolymphoma (T-PL).[19,20] Of note, most T-PLs present as superficial perivascular or band-like dermal infiltrates with or without epidermotropism and rarely as nodular to diffuse dermal-based aggregates.[17] Examples of the latter include mainly arthropod assaults (persistent insect or spider bite reactions and chronic nodular scabies), tattoo ink–related T-PL (individual cases), and rarely drug-related and idiopathic T-PLs. These commonly show admixed eosinophils to varying degrees (except in tattoo ink–related T-PL), coupled with subtle to profound epithelial changes (spongiosis, acanthosis, and/or ulceration-excoriation), and the diagnosis is usually simple after an in-depth clinical interrogation.[21] While true lymphoid neoplasms are rare within this subcategory, TCR-PCR analysis may be useful in ambiguous cases because most infiltrates herein will show polyclonal results. Nevertheless, an isolated monoclonal result should not be considered indicative of lymphoma without adequate clinical, histopathological, and immunophenotypic correlation.[3,16,21]

T-cell–dominant dermal-based proliferations of small and medium lymphocytes

Disorders characterized by a T-cell–dominant dermal-based infiltration of small and medium pleomorphic lymphocytes are typically true clonal proliferations and are by far led by mycosis fungoides (MF), the most common PC-L (Table 2).[2] While patch- and plaque-stage MF show a superficial dermal proliferation with epidermotropism, tumor-stage, follicular (FMF), and rare variants such as interstitial (IMF) and granulomatous MF (GMF) display primarily dermal-based proliferations with limited or absent epidermotropism.[22] Tumor-stage MF (an expression of advanced disease) is seen exclusively in patients with concomitant patches and/or plaques of MF, and sometimes there is a history of long-standing MF.[23-26] FMF commonly affects the head, neck, and/or upper torso, as comedonal/acneiform/keratosis pilaris-like lesions and/or erythematous plaques with follicular prominence in early disease; or as indurated plaques, tumors, and rarely erythroderma in advanced disease. It differs histopathologically from conventional MF (CMF) by proliferations centered around and within hair follicles, diverse follicular-epithelial disruptions, scarce or absent epidermotropism, and varying numbers of admixed eosinophils.[24] IMF and GMF show interstitial aggregates of pleomorphic lymphocytes coupled with a significant histiocytic component in the latter.[25,26] PC-CD8$^+$ aggressive epidermotropic cytotoxic T-cell lymphoma (PC-CD8$^+$ AECTCL), one of the rarest PC-Ls, merits mentioning here because a deep dermal component commonly accompanies the small- to medium-sized superficial and epidermotropic CD8$^+$ T-cytotoxic proliferation characteristic of the disease.[27-29] The highly aggressive clinical course of PC-CD8$^+$ AECTCL differs from that of CD8$^+$ MF and lymphomatoid papulosis (LyP) type D, which additionally shows CD8/CD30 co-expression by clusters of large cells.[2]

Within this category, 2 uncommon neoplasms—adult T-cell leukemia/lymphoma (ATCLL) and rarely T-cell acute lymphoblastic leukemia/lymphoma (T-ALL)—have also been reported to involve the dermis, as small and medium proliferations of mature T cells or T-cell lineage-committed lymphoblasts, respectively (Table 2).[30-34] ATCLL affects chiefly Japanese, African, Caribbean, and South American middle-aged adults infected with human T-lymphotropic virus 1 (HTLV-1). Commonly, it involves the skin in its primary cutaneous tumoral, chronic, and smoldering forms and may be histopathologically indistinguishable from CMF; therefore, their distinction relies largely on CD25/forkhead box protein 3 (FOXP3) expression, proof of HTLV-1 proviral integration within neoplastic cells, and a careful clinical correlation.[30-33] T-ALL ordinarily affects

children and may exceptionally involve the dermis; the blastic nature of infiltrating lymphocytes, however, is not always obvious, and along with a high index of suspicion, the pathologist must rely on terminal deoxynucleotidyl transferase (TdT) and/or CD99 expression by neoplastic cells to reach a proper diagnosis.[34] Lastly, blastic plasmacytoid dendritic cell neoplasm, a rare aggressive neoplasm derived from precursor plasmacytoid dendritic cells and not from T or NK cells, is worth mentioning because it commonly involves the dermis as small- to medium-sized cell proliferations and expresses CD4 and CD56 antigens (generally attributed to T-helper and NK

TABLE 2 T-cell dominant and T-cell predominant B-cell rich, dermal-based proliferations of small and medium lymphocytes

Disease	Typical clinical presentation	Major histopathological features	Immunophenotypic and molecular features
T-cell dominant, dermal-based proliferations of small and medium lymphocytes			
Mycosis fungoides *"tumor stage"*	1 or + (≥1cm) nodules preceded by patches & plaques; + on sun-shielded skin	Dense DP (±SC) of pleomorphic cells w/ <25% "large-sized"	↑ CD4:CD8, βF1+; clonal T-cell population (75-100%)
Mycosis fungoides *"follicular variant"*	Indurated pruritic plaques + follicular accentuation, coalescent follicular papules &/or acneiform lesions; + on head & neck	Dermal peri- & intra-follicular proliferation ± follicular mucinosis ± follicular cystic changes	↑ CD4:CD8; clonal T-cell population (~88%)
Mycosis fungoides *"IMF & GMF"*	Patches & plaques (rarely tumors) identical to those of CMF; + on sun-shielded skin	Histiocytic aggregates (≥25%) + peri-vascular/adnexal & interstitial aggregates of atypical lymphocytes	↑ CD4:CD8, βF1+; clonal T-cell population (~40-90%)
PC-CD8+ aggressive epidermotropic cytotoxic TCL	Rapidly progressing plaques/tumors + ulceration; generalized ± mucosal involvement	PV to nodular DP + epidermotropism + necrotic keratinocytes	CD8+, βF1+, TIA-1+; clonal T-cell population (most cases)
Adult T-cell leukemia/ lymphoma	+ HTLV-1 infection; disseminated macules, papules, nodules, plaques &/or erythroderma	PV, nodular or diffuse DP of pleomorphic lymphocytes with frequent epidermotropism and adnexotropism	↑ CD4:CD8, CCR4+, CD25+; Clonal T-cell population (~ 40%) HTLV-1 proviral integration within host genome
T-cell acute lymphoblastic leukemia/ lymphoma	Solitary (~70%) or multiple red-bluish nodules; + on head & neck	Dense nodular-diffuse dermal (± SC) monomorphous proliferation of small-medium	TdT+, CD99+; ~50-70%: Inv(14)(q11;q32) &/or deletion in chrs 9, 10 or11
Blastic plasmacytoid dendritic cell neoplasm	Multiple (>60%) or single, red-violaceous patches, plaques or tumors; + on scalp, face, trunk & extremities	Non-epitheliotropic diffuse DP of medium-sized cells + peri-vascular/-adnexal accentuation; ± RBC extravasation	CD4+,CD56+,CD123+,TCL1+ *Negative for MPO, lysozyme & CD117*
T-cell predominant B-cell rich, dermal-based proliferations of small and medium lymphocytes			
PC-small medium CD4+ T-cell LPD	Solitary slow-growing plaque or nodule in the absence of history or clinical lesions of MF or SS; + on face, neck or trunk	Dense non-epitheliotropic DP of pleomorphic lymphocytes, <30% "large-sized", + inflammatory cells	CD3+, CD4+, PD1+, ICOS+, CXCL-13+, bcl-6+ & CD10+; Clonal T-cell population (~60%)
PC-acral CD8+ TCL	Solitary slow-growing papule, nodule or plaque; + on acral skin	Dense non-epitheliotropic DP of mostly monomorphic lymphocytes + inflammatory cells	CD3+, CD8+, TIA-1+, βF1+, CD45RO+; Clonal T-cell population (~90%)
Hydroa vacciniforme-like LPD	+ chronic EBV infection; chronic & relapsing papules, vesicles, ulcers, scars & facial edema; + on sun-exposed skin	PV to dense DP (± SC) of pleomorphic cells + epidermal necrosis + dense inflammatory infiltrate	CD3+/CD8+/TIA-1+ or CD56+, EBER+ in a subset of cells Clonal T-cell population (~50%)
Angioimmunoblastic T-cell lymphoma	Rapidly progressive & disseminated macules, papules, nodules &/or plaques; + on the extremities & trunk	Superficial, superficial & deep or nodular-diffuse DP of pleomorphic lymphocytes + admixed inflammatory cells	CD3+, CD5+, PD-1+, CXCL-13+, bcl-6+ ± EBER+ cells Clonal T-cell population (~76%)

White & gray rows indicate "primary cutaneous lymphomas (PC-L)"; green rows indicate "cutaneous lymphomas either primary to the skin or systemic with secondary cutaneous dissemination"; blue rows indicate "systemic lymphomas with secondary cutaneous involvement"; +, indicates positive, predominance, or "more in/on"; ±, with or without; ~, indicates "approximately". Abbreviations: chrs, chromosomes; CMF, conventional mycosis fungoides; DP, dermal proliferation; EBER, Epstein–Barr virus encoded small RNA's demonstration by in situ hybridization EBV, Epstein-Barr virus; GMF, granulomatous mycosis fungoides; HTLV-1, human T-cell leukemia/lymphoma virus type 1; IMF, interstitial mycosis fungoides; inv, inversion; PC-, primary cutaneous; PV, perivascular; RBC, red blood cell; SC, subcutaneous involvement; SS, Sézary syndrome.

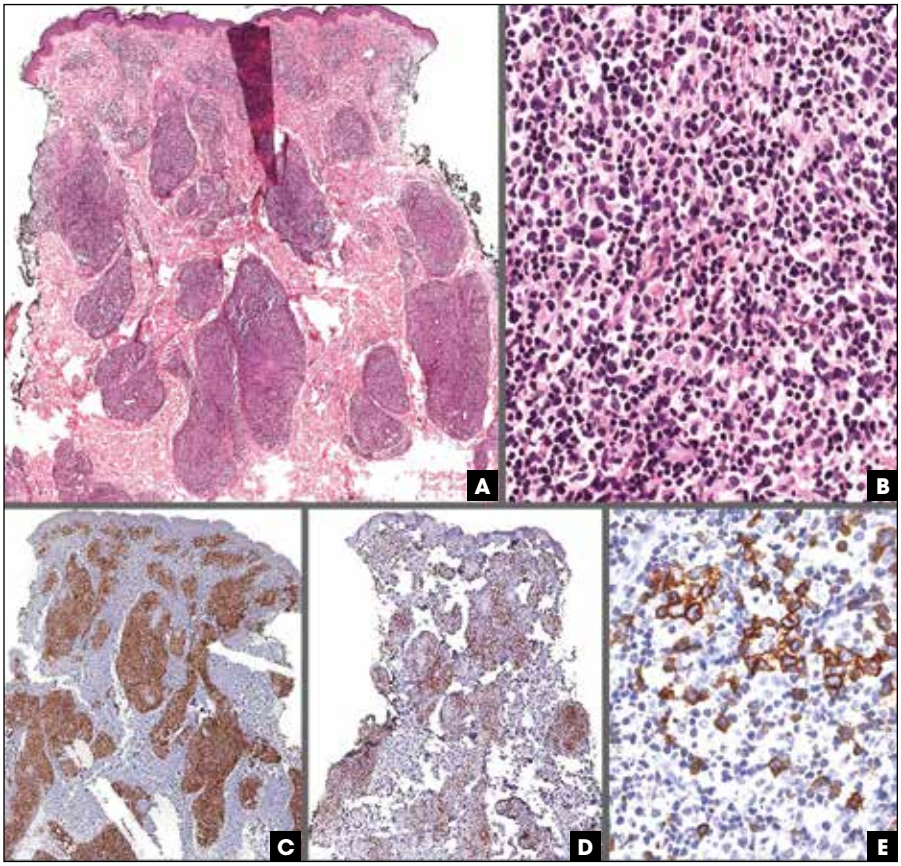

FIGURE 3. Example of T-cell–predominant B-cell–rich dermal-based proliferation of small and medium lymphocytes (PC-SMCD4⁺LPD). (A, B) Hematoxylin & eosin–stained slides, 20x and 200x, respectively; nodular and periadnexal proliferation of small and medium pleomorphic lymphocytes. **(C)** CD4 immunostain (20x) showing a predominance of CD4⁺ T cells. **(D)** CD20 immunostain (20x) showing a minority of reactive B cells. **(E)** PD-1 immunostain (400x) showing PD-1⁺ cells aggregating in the form of rosettes. Abbreviation: CD4, cluster of differentiation 4; PC-SMCD4⁺LPD, primary cutaneous small medium CD4⁺ T-cell lymphoproliferative disorder; PD-1, programmed cell death protein 1.

cells, respectively), along with plasmacytoid dendritic cell lineage antigens (CD123, T-cell lymphoma protein 1 [TCL1], etc).[35-38]

T-cell–dominant and T-cell–predominant B-cell–rich dermal-based proliferations of small and medium lymphocytes

The archetype of dermal-based T-cell–predominant B-cell–rich proliferations is PC small medium CD4⁺ T-cell lymphoproliferative disorder (PC-SMCD4⁺LPD; Figure 3). This condition was formerly called small medium CD4⁺ pleomorphic T-cell "lymphoma," but the name was revised in the 2016 WHO revision of lymphomas to be called PC small medium CD4⁺ T-cell lymphoproliferative disorder. After MF, PC-SMCD4⁺LPD is currently recognized as one of the most common PC T-cell proliferations (along with CD30⁺ LPDs) and is characterized by a single (rarely >1), slow-growing small plaque or nodule, in the absence or history of MF. Histopathologically, it is composed of atypical small to medium pleomorphic T cells, in a nodular to diffuse arrangement with periadnexal accentuation, amidst numerous histiocytes and small B cells. Atypical T cells display a follicular helper T-cell phenotype with CD3/CD4/B-cell lymphoma 6 protein (BCL6) co-expression and immunoreactivity with antibodies against programmed cell death protein 1 (PD-1; forming peculiar rosettes).[39-45] While tumor-stage MF is typically B-cell poor, it is paramount to clinically exclude it because it may be histopathologically indistinguishable from PC-SMCD4⁺LPD and requires aggressive treatment.[2] PC-acral CD8⁺ T-cell lymphoma—a recently described, considerably less common neoplasm—is clinically and histomorphologically identical to PC-SMCD4⁺LPD, albeit occurring mostly on acral sites, with neoplastic cells displaying a CD8⁺ cytotoxic phenotype; it must also be clinically distinguished from rare CD4⁻/CD8⁺ forms of tumor-stage MF.[46-48] Finally, exceedingly rare diseases within this category include cases of cutaneous involvement by angioimmunoblastic TCL (AITCL) and hydroa vacciniforme-like LPD (HV-LLPD).[49-51] Neoplastic cells in AITCL derive from follicular helper T cells and are immunophenotypically indistinguishable from those of PC-SMCD4⁺LPD. By contrast, however, EBER⁺ lymphocytes are present in AITCL, and most patients with cutaneous involvement have numerous, rapidly progressing lesions.[49] HV-LLPD occurs generally in children and young adults with chronic active Epstein-Barr virus (EBV) infection, from Asia and Latin America, as facial edema and chronic and relapsing papules, vesicles, and ulcers on sun-exposed sites. Infiltrating cells display profound angiotropism, cytotoxic markers, CD8 and/or CD56 expression, focal to diffuse EBER⁺, and are found amidst inflammatory cells, including small B cells, along with conspicuous dermal and epidermal changes.[50,51]

T-cell–dominant and T-cell–predominant B-cell–rich dermal-based proliferations of large lymphocytes

Dermal-based proliferations composed chiefly of large T or NK cells (≥4 times the size of a normal lymphocyte) embody true clonal neoplasms ranging from indolent in nature to highly aggressive (Table 3).[2] Indolent proliferations include PC CD30+ LPDs (LyP and PC-anaplastic large cell lymphoma [PC-ALCL]), while all other herein follow an aggressive clinical course, ie, secondary cutaneous involvement by activin receptor-like kinase 1 (ALK-1)⁺ and ALK⁻1⁻ anaplastic large cell lymphoma (SC-ALCL); large-cell transformation (LCT) in tumors of MF, EN NK/TCL nasal type (EN-NK/TCLnt), PC gamma/delta T-cell lymphoma (PC-GDTCL), peripheral T-cell lymphoma not otherwise specified (PTCL-nos); and very rarely, cutaneous involvement by T-cell prolymphocytic leukemia (T-PLL).[2,52,53]

By definition, CD30⁺ LPDs are characterized by aggregates of large CD30⁺ atypical T cells, forming discrete dermal collections

(most forms of LyP) or confluent sheet-like proliferations (LyP type C, PC-ALCL, and SC-ALCL) and invariably require for their distinction detailed clinical information. LyP, the most common proliferation here, is universally characterized by a distinctive clinical course of relapsing and self-healing crops of papules and small nodules, with an excellent prognosis. Numerous clinically indistinguishable histopathological variants have been documented, important given their microscopic similarities with biologically distinct disorders. LyP type A, the most prevalent form, shows aggregates of atypical $CD30^+$ T cells amidst a prominent wedge-shaped inflammatory background, easily confused with benign dermatoses such as PL and arthropod bite reactions. LyP type D differs in its pronounced epidermotropism and $CD8^+$ cytotoxic immunophenotype, mimicking (solely on histopathology) the proliferation of $CD8^+$ MF and PC-$CD8^+$ AECTCL. Similarly, the angiocentric and angiodestructive nature of LyP type E may be misinterpreted as indicative of aggressive angiocentric lymphomas such as EN-NK/TCLnt or even PC-GDTCL because expression of TCR-gamma has been occasionally documented in proven cases of LyP (Figure 4).[2,7,8,54] Follicular LyP shows prominent folliculotropism and follicular epithelial disruptions, akin to FMF; likewise, the newly described form of LyP with 6p25 (DUSP22) chromosomal rearrangements shows a biphasic growth pattern (superficial epidermotropic coupled with dermal aggregates of large cells) comparable to that of MF with LCT.[54,55] In contrast to the rest, LyP type C is characterized by confluent sheets of large atypical $CD30^+$ cells (often representing over 75% of the cellularity) and is histopathologically identical to PC-ALCL and SC-ALCL. PC-ALCL, however, is characterized by rapidly growing, nonresolving solitary tumors (rarely multiple) in the absence of extracutaneous disease; this contrasts with SC-ALCL, which additionally typically shows ALK-1 and epithelial membrane antigen (EMA) immunopositivity.[54] Importantly, however, lack of ALK-1

TABLE 3 T-cell dominant and T-cell predominant B-cell rich, dermal-based proliferations of large lymphocytes

Disease	Typical clinical presentation	Major histopathological features	Typical immunophenotype
T-cell dominant, dermal-based proliferations of large lymphocytes			
Mycosis fungoides *"tumor stage with large cell transformation"*	*Same as for tumor-stage CMF (table 2)*	Same as for tumor-stage CMF but with ≥25% of neoplastic cells being large-sized	*Same as for tumor-stage CMF (table 2)*
Cutaneous anaplastic large cell lymphoma	Rapidly growing solitary (80%) or grouped, red-violaceous tumors (>1.5cm); + on extremities	Dense nodular-diffuse DP (± SC) of large lymphocytes	$CD30^+$ (≥75% of cells); most $CD4^+$ ~33%: IRF4/DUSP22 rearrangements
Lymphomatoid papulosis *"type C"*	Relapsing & remitting crops of papules & small nodules; + on trunk & proximal extremities	Same as for cutaneous anaplastic large cell lymphoma (see above)	*Same as for cutaneous anaplastic large cell lymphoma (see above)*
Extranodal NK-/T-cell lymphoma, nasal type	Rapid onset & progression of ulcerated plaques & nodules; + on face	PV to diffuse DP (± SC) of medium & large-sized cells with prominent angiocentric/destructive growth	$CD3e^+$, $CD56^+$, $TIA\text{-}1^+$, $EBER^+$
Cutaneous γ/δ-T-cell lymphoma	Rapidly progressing multiple (rarely single) erosive or ulcerated plaques & deep-seated nodules	Nodular-diffuse dermal & lobular SC proliferation of variably sized cells	$CD3^+$, $CD56^+$, $GM1^+$, $CD4^-/CD8^-$ ($CD8^+$ ~40%)
Peripheral T-cell lymphoma, nos	Rapidly growing large ulcerated nodules/tumors w/o preceding patches/plaques; disseminated	Nodular-diffuse DP (± SC of variably-sized atypical cells (large-sized ≥30%), w/o epitheliotropism (rarely focal)	Variable $CD4^+$ or $CD8^+$ Clonal T-cell population (~100%)
T-cell prolymphocytic leukemia	Disseminated purpuric nodules, facial edema &/or erythroderma	Superficial or superficial & deep DP of medium-large prolymphocytes	$CD2^+$, $CD3^+$, $CD7^+$; variable $CD4^+$ or $CD8^+$,
T-cell predominant B-cell rich, dermal-based proliferations of large lymphocytes			
Lymphomatoid papulosis *"types A, D, E, follicular & with DUSP22 rearrangements"*	*Same clinical course as described for lymphomatoid papulosis type C (see above)*	- Type A: wedge-shaped DP with clusters of large atypical cells, amidst inflammatory cells - Type D: PSD DP ± SC of medium-sized cells + epidermotropism - Type E: angioinvasive/destructive DP of medium-sized cells - Follicular: = features of type A (rarely B or C) + folliculotropism - With DUSP22 rearrangements: biphasic pattern (type B + type C)	All show clusters of $CD30^+$ cells Type A: $CD4^+$ (rarely $CD8^+$ or $CD56^+$) Types D & E: $CD8^+$, $TIA\text{-}1^+$ With DUSP22 rearrangements: weak superficial & strong dermal $CD30^+$

White & gray rows indicate "primary cutaneous lymphomas"; green rows indicate "cutaneous lymphomas either primary to the skin or systemic with secondary cutaneous dissemination"; blue rows indicate "systemic lymphomas with secondary cutaneous involvement"; +, indicates positive, predominance, or "more in/on"; CMF, conventional mycosis fungoides; DP, dermal proliferation; SC, subcutaneous involvement; ~, indicates "approximately"; EBER, Epstein–Barr virus encoded small RNA's demonstration by in situ hybridization.

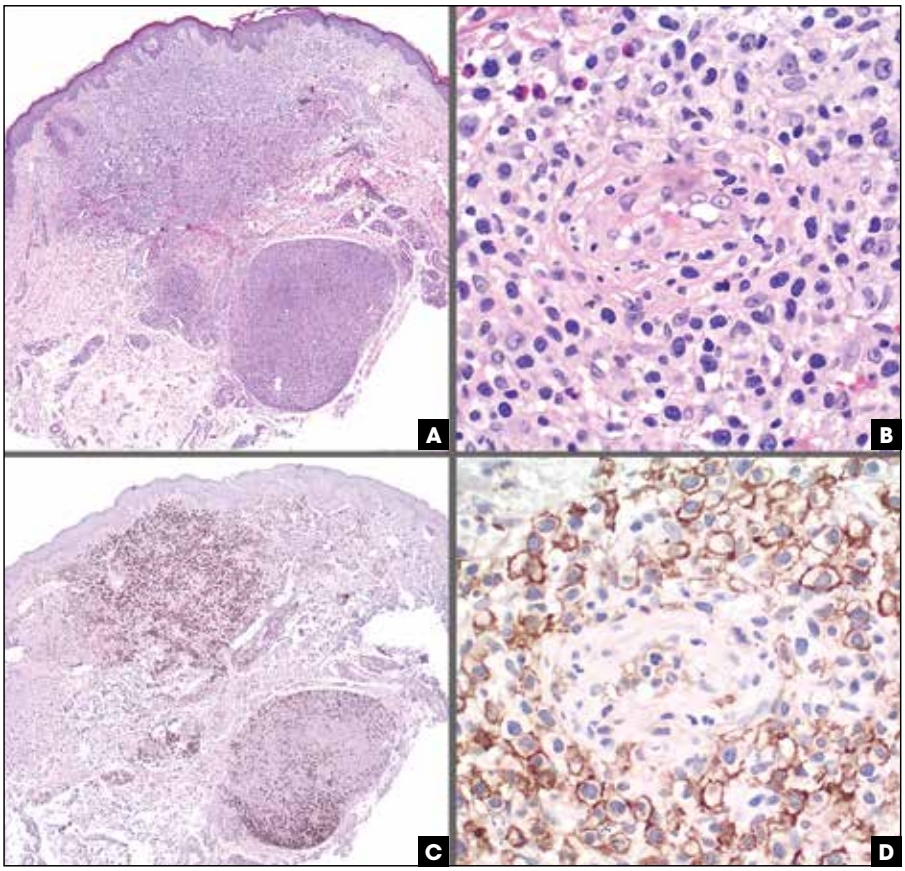

FIGURE 4. Example of T-cell–predominant B-cell–rich dermal-based proliferation of large lymphocytes (LyP type E). (A, B) Hematoxylin & eosin–stained slides, 20x and 400x, respectively; nodular and angiotropic dermal-based proliferation of large lymphocytes, admixed with small reactive lymphocytes and eosinophils. **(C, D)** CD30 immunostain (20x and 400x, respectively) showing nodular and perivascular aggregates of $CD30^+$ large lymphocytes. Abbreviations: CD30, cluster of differentiation 30; LyP, lymphomatoid papulosis.

labeling does not exclude cutaneous involvement from SC-ALCL because some are ALK-1 negative.[56]

Tumors of MF, typically composed of small- and medium-sized lymphocytes, enter the differential diagnosis here, in the context of LCT, characterized by large cells comprising at least 25% of the cellularity. As previously stated, emphasis must be placed on the obligatory presence of preceding patches, plaques, and/or erythroderma for a definitive diagnosis of tumor-stage MF, particularly because CD30 expression is not uncommon in this context, albeit typically limited to less than 30% of the cellularity—in stark contrast to ALCL and LyP type C.[57]

Exceedingly rare cutaneous neoplasms within the large T- and NK cell category must also be considered. Both EN-NKTCLnt and PC-GDTCL are clinically characterized by generalized, rapidly growing plaques and tumors, unpreceded by long-standing patches and/or plaques (in contrast to MF).[58-62] EN-NKTCLnt commonly involves the facial midline area, though cutaneous lesions may appear in any topography, as in PC-GDTCL. While PC-GDTCL tends to involve primarily the subcutis in the form of a lobular panniculitic-like proliferation, dermal involvement is not uncommon, frequently as angiocentric aggregates akin to those in EN-NKTCLnt. Therefore, detailed IHC is paramount for their distinction; cells in both EN-NKTCLnt and PC-GDTCL commonly express CD56 and T-cell intracytoplasmic antigen (TIA-1), the former being CD3ε and EBER positive and the latter CD4/CD8 "double negative" (CD8+ in a small proportion of cases) as well as crucially T-cell receptor Beta F1 (ßF1) negative and ganglioside (GM)1 positive, confirming their gamma-delta lineage.[58-62] PTCL-nos, a diagnosis of exclusion, exceptionally involves the skin (primarily or more frequently secondarily); its clinical and histopathological appearance is diverse, with patients typically presenting with generalized skin plaques, bruise-like lesions, and/or nodules, which appear under the microscope as perivascular to diffuse dermal proliferations of small to medium pleomorphic cells, of variable immunophenotype.[63,64] Finally, within this category are also rare cases of cutaneous involvement from T-PLL, described in older individuals as lesions ranging from edema and nodules to erythroderma, and histopatologically as dermal proliferations of medium to large cells with basophilic cytoplasm and round cleaved nuclei with condensed chromatin and prominent nucleoli (prolymphocytes).[52,53]

B-cell–dominant and B-cell–predominant T-cell–rich dermal-based proliferations of small and medium lymphocytes

Dermal proliferations composed exclusively of small and medium B cells are infrequent because indolent PC B-cell lymphomas (PC-BCLs) are typically accompanied by a conspicuous reactive T-cell population (Table 4).[2] Infrequently, however, such a proliferation may be encountered in cutaneous involvement by chronic lymphocytic leukemia/small lymphocytic lymphoma (CLL) and exceptionally, in lymphoplasmacytic lymphoma (LPL) and mantle cell lymphoma (MCL).[65-71] Cutaneous findings in CLL, LPL, and MCL are largely nonspecific, requiring a high index of suspicion and thorough immunophenotyping to yield a diagnosis. Neoplastic cells in CLL are small and uniform, with coarse chromatin and scant cytoplasm, and characteristically co-express pan–B-cell markers (CD20, CD19, and paired box protein 5 [PAX5]), along with CD5, CD43, and/or CD23.[65-67] Cells in LPL have a lymphoplasmacytic morphology, and—in contrast to CLL—show *kappa* or less often *lambda* monoclonal Igl gene rearrangements; additionally, patients with LPL may present with periodic acid-Schiff $(PAS)^+/IgM^+$ dermal paraprotein deposits (cutaneous macroglobulinosis).[68,69] Finally, dermal involvement by MCL is typically characterized by a monomorphic proliferation of small to medium $CD20^+$, $bcl\text{-}1^+$ (cyclin-D1), and SRY-related HMG-box $(SOX)11^+$ cells.[70-72]

B-cell–dominant T-cell–rich dermal-based infiltrates and prolif-

erations of small and medium lymphocytes are the hallmark of B-cell pseudolymphoma/cutaneous lymphoid hyperplasia (CLH) and low-grade PC-BCLs, ie, marginal zone lymphoma (PC-MZL)—lumped under the term "extranodal marginal zone lymphoma of mucosa-associated lymphoid tissue or MALT lymphoma" in the 2016 WHO revision—and follicle center lymphoma (PC-FCL).[2-4,21] CLH shows striking clinicopathological similarities with low-grade PC-BCLs, all of which appear as single or multiple red to violaceous, slow-growing nodules, predominantly affecting face, trunk, or upper extremities. CLH tends to affect young patients and follows a self-limited course in contrast to PC-MZL and PC-FCL, which mostly occur in middle-aged to older individuals and lack spontaneous resolution. On histology, CLH and low-grade PC-BCLs are characterized by nonepidermotropic, nodular to diffuse, bottom-heavy or top-heavy dermal infiltrates/proliferations, of small and medium B cells, with or without GCs and admixed with inflammatory cells (reactive T cells, histiocytes, and granulocytes)—which, in abundance and particularly when coupled with reactive epidermal changes, favor CLH.[73-78] Morphological attributes in favor of PC-MZL include confluent aggregates of plasma cells or lymphoplasmacytoid cells (regularly at the margins of the proliferation) and collections of pale-staining medium-sized cells with indented nuclei (marginal-zone or centrocyte-like cells), surrounding aggregates of small and dark-staining lymphocytes.[78-80] By contrast, PC-FCL shows a prolif-

TABLE 4 B-cell dominant and B-cell predominant T-cell rich, dermal-based infiltrates and proliferations of small and medium lymphocytes

Disease	Typical clinical presentation	Major histopathological features	Typical immunophenotype
B-cell dominant, dermal-based proliferations of small and medium lymphocytes			
Chronic lymphocytic leukemia/small lymphocytic lymphoma	Solitary, grouped or generalized papules, nodules or plaques; + on face	DP of small, uniform cells w/ coarse chromatin & scant cytoplasm	CD20+, CD19+, PAX-5+, CD5+, CD43+ & CD23+
Lymphoplasmacytic lymphoma	Nodules or plaques; + on trunk, face, neck & scalp	PV, PA & interstitial DP of small-medium lymphoplasmacytic cells	CD19+, CD20+, CD22+, CD79a+, PAX-5+ κ (+ often) or λ *mc-Igl rearrangement*
Mantle cell lymphoma	Disseminated nodules, macules, papules and/or plaques; + on trunk, face, extremities & scalp	Nodular-diffuse DP + PV/PA accentuation of momomorphic or pleomorphic small-medium (rarely large) cells w/irregular nuclei	CD20+, CD5+, bcl-1+, SOX11+
B-cell acute lymphoblastic leukemia/lymphoma	Single or multiple erythematous nodules or plaques; + in scalp, face & trunk	PV, PA, nodular or diffuse DP (± SC) of variably sized B-cell lineage-committed lymphoblasts	CD19+, CD79a+, CD22+, PAX-5, TdT+, CD10+
B-cell predominant T-cell rich, dermal-based proliferations of small and medium lymphocytes			
Cutaneous lymphoid hyperplasia	Self-resolving red-violaceous papules or nodules; + on face chest & PE	Follicular and/or diffuse infiltrate of small lymphocytes admixed with scattered medium-sized cells.	B-cells: CD19+, CD20+, CD22+, CD79a+; polytypic κ & λ light chains; mc-IgH rearrangement (~10% of cases)
PC-marginal zone lymphoma	Solitary or multiple, red-violaceous papules, nodules or plaques; + on trunk & PE	DP (± SC) of small lymphocytes, centrocyte-like marginal zone cells* & lymphoplasmacytoid & plasma cells	CD20+, CD79a+, bcl-2+; κ (+ often) or λ restriction (≥ 5:1) in ~85%; + mc-IgH rearrangement in ~60-70%
PC-follicle-center lymphoma	Solitary/clustered, red-violaceous papules, nodules and/or plaques; + on head, neck, trunk	Follicular &/or diffuse DP (± SC), of variably sized centrocyte-like cells* admixed with scattered centroblast-like cells**	CD20+, CD79a+, PAX5+, bcl-6+; + mc-IgH rearrangement (~90%)
Follicular lymphoma	Multiple (rarely solitary) red-violaceous papules or nodules; + on head & neck	*Same as for PC-follicle-center lymphoma (see above)*	*Same as for PC-FCL (see above)* except for frequent bcl-2+; t(14;18) in most cases; + mc-IgH (~90%)
Lymphomatoid granulomatosis	Disseminated nodules, papules and/or plaques	PV & PA DP (± SC) of variably sized cells admixed with numerous reactive cells	Tumor cells: CD20+, variable EBER+

Blue rows indicate "systemic lymphomas with secondary cutaneous involvement"; green rows indicate "cutaneous lymphomas either primary to the skin or systemic with secondary cutaneous dissemination"; pink rows indicate "benign lymphocytic infiltrates"; white & gray rows indicate "primary cutaneous lymphomas (PC-L)"; +, indicates positive, predominance, or "more in/on"; w/, with; DP, dermal proliferation; PV, perivascular; PA, periadnexal; mc-Igl, monoclonal immunoglobulin light chain-gene; k, kappa; l, lambda; PE, proximal extremities; ~, indicates "approximately"; PC, primary cutaneous; SC, subcutaneous involvement; * small slightly elongated lymphocytes with indented nuclei & no nucleolar prominence; ** medium to large round lymphocytes with vesicular nuclei and 2 or more peripheral nucleoli.

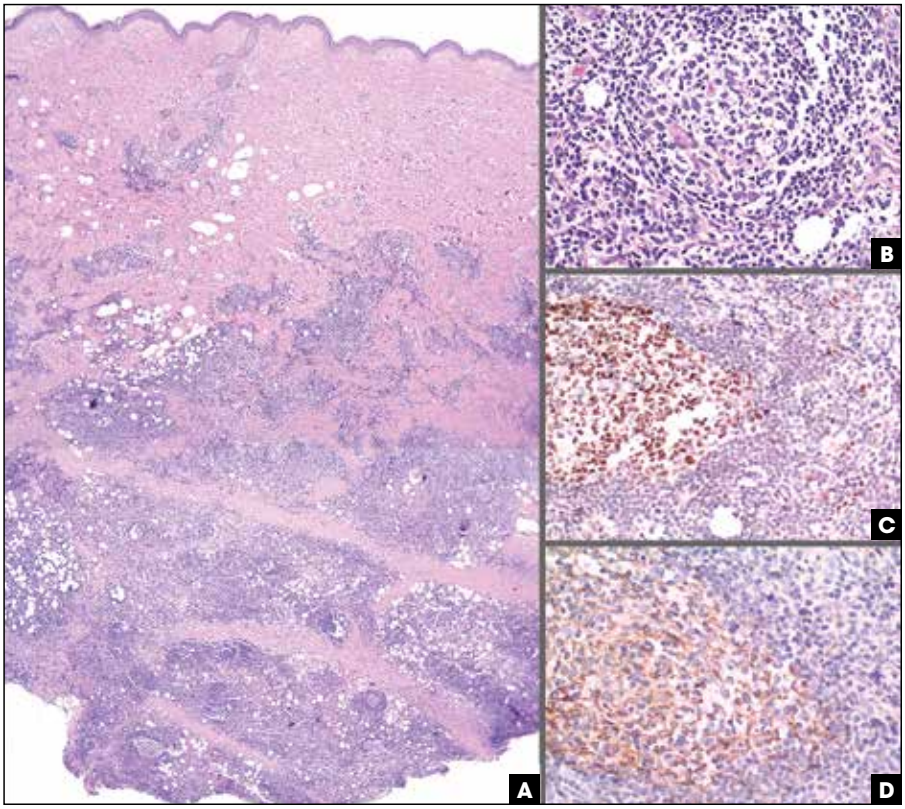

FIGURE 5. Example of B-cell–predominant T-cell–rich dermal-based proliferation of small and medium lymphocytes (primary cutaneous follicle-center lymphoma). (A, B) Hematoxylin & eosin–stained slides, 20x and 200x, respectively; nodular to diffuse dermal-based proliferation of small and medium lymphocytes with aberrant GCs. **(C)** bcl-6 immunostain (200x) showing bcl-6$^+$ B cells within and outside a GC. **(D)** CD21 immunostain (200x) showing dendritic reticulum cells within a GC. bcl-6, B-cell lymphoma 6 protein; CD21, cluster of differentiation 21; GC, germinal center.

eration of chiefly centrocyte-like cells, admixed with occasional centroblasts (medium-sized cells with 2 or more peripheral nucleoli), small reactive lymphocytes, and a scarcity of immunoblasts (large-sized cells with central nucleoli; Figure 5). When present in PC-FCL, GCs commonly show aberrancies in their architecture (size and shape variability and/or confluence) and composition (reduced or absent mantle zone and paucity of tingible body macrophages); furthermore, aggregates of centrocytes and/or centroblasts between or outside GCs strongly favor the diagnosis of PC-FCL over CLH and PC-MZL.[78-83] By IHC, cells in CLH and low-grade PC-BCLs express pan–B-cell markers, amidst a smaller population of reactive CD3$^+$ T cells. Neoplastic B cells in PC-MZL are bcl-2+ and bcl-6–, in contrast to those of PC-FCL, which lack bcl-2 expression (positive in a small subset) but universally express GC B-cell markers (bcl-6 ± CD10). GC B-cell markers also highlight the aberrant localization of neoplastic cells outside GCs in PC-FCL, as opposed to CLH and PC-MZL, especially when comparing such stains (in parallel or thorough double immunostaining) against sections stained with anti-CD21 or -CD23 antibodies (markers of dendritic reticulum cells, helpful in identifying the architecture and presence of often indiscernible residual follicles). GCs, when present in CLH and PC-MZL, are reactive in nature and display a high (≥90%) Ki67 proliferation index, as opposed to the low proliferation index (<50%) within GCs in PC-FCL.[2,3,78-81] Despite morphological and immunophenotypical differences, more sensitive techniques are often required to distinguish CLH from low-grade PC-FCLs, and PC-MZL from PC-FCL. Monotypic Igl restriction in plasma cells and/or lymphoplasmacytoid cells by ISH (or IHC) is by far the most reliable indicator in favor of PC-MZL; if ISH shows a polytypic kappa:lambda ratio, monoclonal immunoglobulin heavy-chain rearrangements support PC-FCL over CLH; nonetheless, some cases of archetypical CLH (approximately 10%) display monoclonality ("clonal CLH"), compelling a close follow-up of afflicted patients.[2,3,83] Cutaneous involvement by nodal follicular lymphoma (FL) is histopathologically indistinguishable from PC-FCL, although by IHC most FLs express bcl-2, reflecting the t(14:18) chromosomal translocation, as opposed to PC-FCL. However, as rare cases of bcl-2+ PC-FCL have been described, distinction between PC-FCL and FL must always rely on complete staging at diagnosis, to rule out extracutaneous lymphoma.[84]

Finally, cutaneous involvement by lymphomatoid granulomatosis, a rare EBV-related B-cell LPD, must be also considered when approaching angiocentric dermal-based proliferations of small to medium (occasionally large) B cells (with variable EBER$^+$) intermingled with numerous histiocytes and reactive T cells.[85]

B-cell–dominant and B-cell–predominant T-cell–rich dermal-based proliferations of large lymphocytes

Primary cutaneous dermal-based B-cell–dominant proliferations of large lymphocytes are uncommon (Table 5) because most PC-L arise from T cells, and those derived from B cells are significantly outnumbered by low-grade PC-BCLs; typically composed of small and medium lymphocytes.[73] When large B cells predominate, the PC archetype is diffuse large B-cell lymphoma of the leg (PC-DLBCL-lt), morphologically indistinguishable from the rarer PC-DLBCL not otherwise specified (PC-DLBCL-nos).[86,87] By contrast, the differential diagnosis is broader amongst nodal and extracutaneous large-sized B-cell lymphomas that may occasionally involve the skin; it includes DLBCL-nos, plasma cell myeloma (PCM), EBV$^+$ DLBCL, intravascular large B-cell lymphoma (IV-LBCL), plasmablastic lymphoma (PBL), primary effusion lymphoma (PEL), Burkitt lymphoma (BL), and very rarely B-cell ALL (B-ALL).[4] Finally, while most lymphomas herein are characterized by a dominant B-cell proliferation, HL differs by the abundance of reactive T cells amidst the often-scarce, large B-cell neoplastic proliferation.[88]

PC-DLBCL-lt, a neoplasm of intermediate biological behavior, usually affects elderly women as rapidly growing often ulcerated tumors, commonly on lower extremities. Upon microscopy, it is

characterized by a dermal proliferation of mitotically active immunoblasts (ie, large-sized bcl-2$^+$, multiple myeloma oncogene 1$^+$, FOX-1$^+$, IgM$^+$ B cells with central nucleoli), lacking GCs and/or remnants of follicular dendritic networks (FDNs), typical of PC-FCL (Figure 6).[88,89] Rarely, however, PC-FCL with a diffuse growth pattern (described under the small- and medium-sized B-cell category) may also lack GCs and/or FDNs and display a predominance of medium to large cells. In this scenario, PC-FCL may mimic the proliferation of PC-DLBCL-lt; in contrast, however, neoplastic cells in PC-FCL are centroblasts, strongly express bcl-6 (absent or focal in PC-DLBCL-lt), and lack bcl-2 and IgM expression, and only a minority (<30%) will label with MUM-1.[3,86,87] Finally, in the absence of a specific nomenclature, rare primary cutaneous dermal-based proliferations of neoplastic large B cells that fail to label with antigens that define PC-DLBCL-lt are currently lumped under the category of PC-DLBCL-nos.[86]

TABLE 5 B-cell dominant and B-cell predominant T-cell rich, dermal-based proliferations of large lymphocytes

Disease	Typical clinical presentation	Major histopathological features	Typical immunophenotype
Primary cutaneous B-cell dominant, dermal-based proliferations of large lymphocytes			
PC-diffuse large B-cell lymphoma, leg type	Rapidly growing red-violaceous nodules/tumors or plaques, frequently ulcerated; + on LE (~ 71-85%)	Diffuse/confluent DP (± SC) of large centroblast- & immunoblast-like cells	CD19$^+$, CD20$^+$, CD22$^+$, CD79a$^+$, PAX5$^+$, bcl-2$^+$, MUM1+ mc-IgH rearrangement
PC-diffuse large B-cell lymphoma, nos	Rapidly growing, single (rarely multiple), tumors or plaques, frequently ulcerated; + head & neck	*Same as for PC-diffuse large B-cell lymphoma-leg type (see above)*	CD19$^+$, CD20$^+$, CD22$^+$, CD79a$^+$, PAX5$^+$, bcl-6$^+$, bcl-2$^-$ mc-IgH rearrangement
Secondary cutaneous (rarely primary cutaneous) B-cell dominant, dermal-based proliferations of large lymphocytes			
Diffuse large B-cell lymphoma, nos *"ABC & GCB"*	Single or multiple, red-violaceous nodules/tumors or plaques; on any topography	*Same as for PC-diffuse large B-cell lymphoma-leg type (see above)*	All: CD19$^+$, CD20$^+$, CD79a$^+$, PAX5$^+$, mc-IgH rearrangement; GCT: CD10$^+$ or CD10$^-$/MUM1-/bcl-6$^+$; ABC: MUM1$^+$, bcl-2$^+$;
EBV diffuse large B-cell lymphoma	Multiple lesions (rarely single): palpable erythema, papules, nodules; + on trunk, neck & upper limbs	Diffuse polymorphic DP of immunoblast-, plasmablast- or Reed-Stenberg-like cells + reactive plasma cells & histiocytes	CD45$^+$, CD19$^+$, CD22$^+$, CD79a$^+$, PAX5$^+$, MUM1$^+$, EBER$^+$ mc-Igl rearrangement
Intravascular large B-cell lymphoma	Livedo-like reticular erythema, telangiectasias, and/or panniculitic-like tumors; + on trunk & extremities	Dermal (± SC), intravascular proliferation of large centroblast- & immunoblast-like cells	CD19$^+$, CD20$^+$, CD22$^+$, CD79a$^+$, PAX5$^+$ mc-IgH rearrangement
Plasmablastic lymphoma	+ in immunodeficient ♂; solitary/grouped, red-violaceous tumors; + trunk & extremities	Multinodular-diffuse DP of large plasmablast- or immunoblast-like cells + apoptotic bodies	CD38$^+$, CD138$^+$, CD20$^-$, PAX5$^-$ *EBER$^+$ (~64-75%); ± HHV8$^+$ (LANA1)*
Extracavitary primary effusion lymphoma	+ in HIV+ ♂; cutaneous nodules/tumors ± concomitant cavitary effusions	Nodular-diffuse DP of large plasmablastic-, immunoblastic-, or anaplastic-like cells, ± intravascular invasion	CD45$^+$, CD38$^+$, CD138$^+$, CD19$^-$, CD20$^-$, HHV8+ (LANA1); mc-Igl rearrangement ± EBER+ (~78%-90%)
Burkitt's lymphoma	Single or multiple erythematous nodules; + on head/neck & trunk	Multinodular-diffuse DP of medium-large monomorphous blastoid-like cells, + numerous apoptotic cells	CD20$^+$, CD79a$^+$, PAX5$^+$, CD10$^+$, bcl-6$^+$, IgM$^+$, MYC+ (Y69), TCL1+; mc-Igl rearrangement, *MYC* rearrangements (100%)
Plasma cell myeloma	Solitary or clustered red-violaceous papules, nodules, or plaques; on any topography	Nodular, interstitial or diffuse DP (± SC) of medium-large pleomorphic neoplastic plasma cells	CD38$^+$, CD138$^+$; mc-Igl rearrangement
B-cell predominant T-cell rich, dermal-based proliferations of large lymphocytes			
Hodgkin lymphoma *"Classic Hodgkin lymphoma"*	Single or agminated papules, nodules or plaques; + on axillae & chest	Nodular or interstitial DP (± SC) of few large mono- or multi-nucleated cells w/ prominent nucleoli, + inflammatory cells	CD30+, PAX5+, CD15+; mc-Ig rearrangement after single cell enrichment in most cases

White & gray rows indicate "primary cutaneous lymphomas"; blue rows indicate "systemic lymphomas with secondary cutaneous involvement"; green rows indicate "cutaneous lymphomas either primary to the skin or systemic with secondary cutaneous dissemination"; PC, primary cutaneous; +, indicates positive or "more in/on"; ~, indicates "approximately". Abbreviations: ABC, activated B-cell type; DP, dermal proliferation; EBER, Epstein–Barr virus encoded small RNA's demonstration by in situ hybridization; GCT, germinal center type; HHV8, human herpes virus 8; HIV, human immunodeficiency virus; SC, subcutaneous involvement; w/, with; w/o, without; ±, with or without; mc-IgH, monoclonal immunoglobulin heavy chain-gene; nos, not otherwise specified"; mc-Igl, monoclonal immunoglobulin light chain-gene.

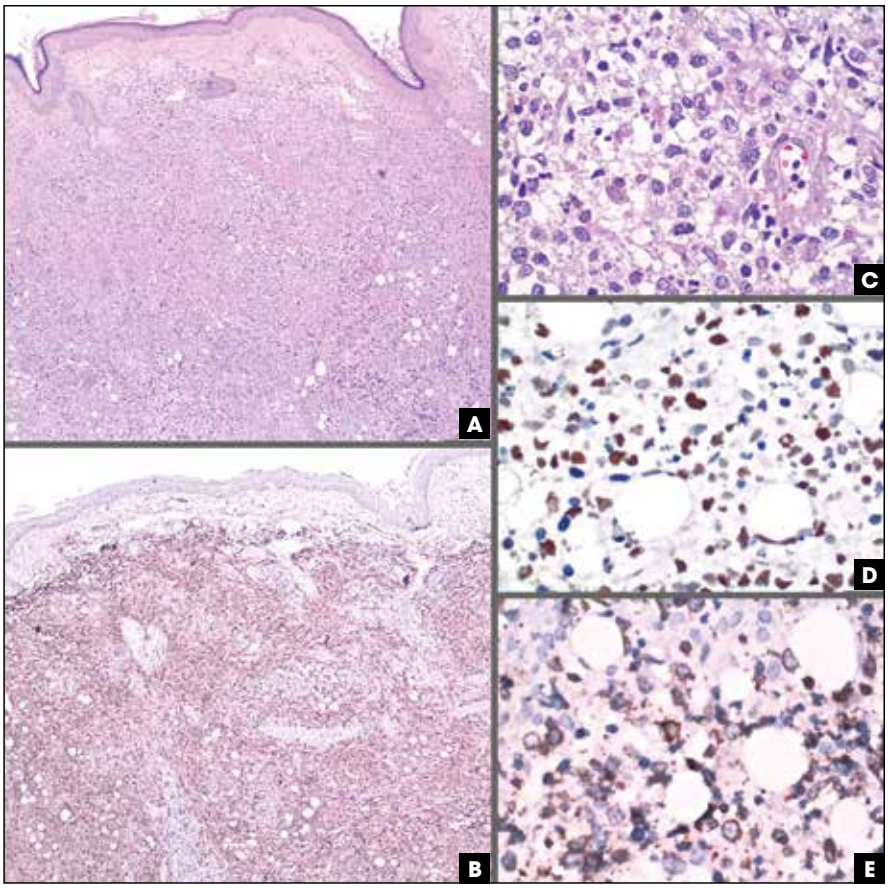

FIGURE 6. Example of B-cell–dominant dermal-based proliferation of large lymphocytes (PC-DLBCL-lt). (A, C) Hematoxylin & eosin–stained slides, 20x and 200x, respectively; diffuse dermal-based proliferation of large lymphocytes with prominent central nucleoli (immunoblasts). **(B)** CD20 immunostain (20x) showing diffuse immunoreactivity. **(D)** MUM-1 immunostain (200x) showing nuclear immunostaining in most neoplastic lymphocytes. **(E)** bcl-2 immunostain (200x) showing cellular immunostaining in neoplastic cells. bcl-2, B-cell lymphoma 2 protein; CD20, cluster of differentiation 20; multiple myeloma oncogene 1; PC-DLBCL-lt, primary cutaneous diffuse large B-cell lymphoma leg type.

Amidst the vast list of large-sized B-cell extracutaneous lymphomas that may secondarily involve the skin (defined by staging procedures as extracutaneous lymphoma preceding or present at the time of cutaneous disease), DLBCL-nos is by far the most common neoplasm.[90] Identical in histomorphology to its PC counterpart, DLBCL-nos is subdivided for prognostic reasons into "activated B cell" (ABC) and "germinal center B cell" (GCB) subtypes, following the Hans IHC algorithm; ABC-type DLBCL-nos strongly expresses bcl-2 and MUM1 (akin to PC-DLBCL-lt), while GCB-type DLBCL-nos is $CD10^+$ or $CD10^-/MUM1^-/BCL6^+$.[4,91] Of note, the 2016 WHO revision introduced the term "high-grade B-cell lymphoma" (HGBL) as a new category, distinct form DLBCL-nos, for all large-BCLs with *MYC* and *BCL2* and/or *BCL6* rearrangements ("double-/triple-hit" lymphomas). However, the incidence of cutaneous involvement by these HGBL in contrast to DLBCL-nos is currently unclear.[4,92] PCM, one of the most common neoplasms of mature large B cells, may primarily or secondarily involve the skin. Cutaneous involvement occurs as solitary or clustered papules, nodules and/or plaques, and is characterized by a dermal proliferation of pleomorphic cells that typically express CD38 and CD138 while lacking pan–B-cell antigen expression.[93] Within this category are also sporadic cases of cutaneous involvement from rare lymphomas that mostly occur in peculiar clinical scenarios; ie, EBV-DLBCL (in EBV-infected patients without immunosuppression other than senescence-related), IV-LBCL (occurring within small vessels and often accompanied by neurologic or multiorgan-failure–related symptoms), PBL (mostly in HIV^+ immunodeficient men), PEL (in immunocompromised or elderly Mediterranean patients and strongly associated with human herpes virus-8 infection), BL (in African children or immunosuppressed men), and B-ALL (occurring mostly in children from Latin America).[4,87,94-101] Lastly, HL, the archetype of B-cell–predominant T-cell–rich proliferations of large lymphocytes, tends to affect children and young adults, and cutaneous involvement has been described, particularly in its "classic" histopathological subtype, as dermal proliferations of hyperlobulated neoplastic mono- or multinucleated $CD30^+$, $PAX5^+$, and $CD15^+$ cells, amidst a prominent inflammatory background.[88]

Summary

Dermal-based lymphoid infiltrates and proliferations include a vast list of differential diagnoses, including common reactive dermatoses and indolent lymphoid proliferations as well as primary and secondary cutaneous lymphomas. Considering the significant overlap in their clinical, histopathologic, and immunophenotypic features, we propose a simplified diagnostic approach relying on the overall B- versus T-cell lymphocytic composition, in conjunction with the predominant cytomorphology (cell size). Nevertheless, a final diagnosis must be based on a multiparameter approach integrating clinicoimmunopathologic correlation and, in selected cases, molecular studies.

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