Updated Classification of Cutaneous Lymphoma

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Abstract: The International Consensus Classification (ICC) of myeloid and lymphoid neoplasms follows the precedent set in the Revised European-American lymphoma classification for modern lymphoma classifications by defining specific diseases on the basis of all the available morphologic, immunophenotypic, genetic, and clinical findings. Primary cutaneous lymphomas exhibit a broad range of clinical behavior ranging from lesions which spontaneously regress to those which run an aggressive, often fatal course. Accurate separation of entities is therefore essential for prognostication and to ensure appropriate treatment is administered. However, despite marked differences in clinical course, many subtypes of primary cutaneous lymphoma exhibit remarkably similar, often overlapping, and sometimes indistinguishable pathologic features. While molecular analysis has furthered our understanding of some of these disease entities, it does not yet facilitate robust distinction. Thus, clinical correlation retains a central role in both the diagnosis and classification of primary cutaneous lymphoma. This review aims to draw attention to problem areas in differential diagnosis and hopefully offer some practical suggestions for resolving difficult cases. It will also highlight recent advances in the field and discuss how they reinforce the current classification system and how they might impact of future classifications and treatment strategies.

Key Words: skin, lymphoma, classification, diagnosis

(*Adv Anat Pathol* 2025;32:239–255)

Primary cutaneous lymphomas are defined as lymphomas presenting in the skin in the absence of extracutaneous disease following adequate staging, the latter to include CT scans of chest, abdomen and pelvis, as well as bone marrow biopsy. The one exception to this is Sézary syndrome in which involvement of peripheral blood is part of the constellation of features required for diagnosis. Entities listed in the International Consensus Classification (ICC) can be grouped into lymphomas that run an essentially benign clinical course, those with generally indolent growth but with potential for progression to more aggressive disease in a small percentage of cases, and those which run an aggressive, often fatal course from the outset (Table 1). The term lymphoproliferative disorder (LPD) is now appended to the former group of tumors. These are clonal proliferations of lymphoid cells with the aberrant phenotype and structural or mutational genetic abnormalities (ie, true neoplasms) that behave in an essentially benign fashion and for which the moniker of lymphoma with its connotations of malignancy would not be appropriate.

Despite advances in knowledge and the ever-increasing availability of sophisticated diagnostic techniques, the diagnosis of primary cutaneous lymphoma remains a problematic area. In part, this is because several entities, as currently defined, show similar pathologic features but display radically different clinical behavior with different requirements for treatment. Distinguishing between such lymphomas remains heavily reliant on clinical input, primarily the presenting features and initial clinical course, particularly with entities that preferentially involve the epidermis and superficial dermis, and display a cytotoxic phenotype. This article provides an approach to the diagnosis of primary cutaneous lymphoma, based on the terminology, definitions, and criteria used in the International Consensus Classification, highlighting areas in which clinical correlation remains essential. It will call attention to recent changes in nomenclature together with advances in our understanding of the molecular pathogenesis of this enigmatic group of lymphomas, documenting findings that underpin the current approach to classification and point the way for future classifications and towards potential new novel treatments.

PRIMARY CUTANEOUS B-CELL LYMPHOMA

In the revised fourth edition of the World Health Organization (WHO) classification, there were only 2 neoplasms specifically referenced as primary cutaneous B-cell lymphomas: primary cutaneous follicle center lymphoma (PCFCL) and primary cutaneous diffuse large B-cell lymphoma, leg type (PCDLBCL-LT).[1] While it was recognized that lymphoplasmacytic proliferations of marginal zone type could arise primarily in skin, these were grouped with morphologically similar lymphomas arising at other extranodal sites under a common heading of extranodal marginal zone lymphoma of mucosa-associated lymphoid tissue (MALT lymphoma). A significant change in the ICC, for reasons that will be outlined below, is to recognize MALT-lymphoma-like cutaneous proliferations as distinct from MALT lymphomas arising at other sites, returning to the philosophy of the original 1997 European Organization for Research and Treatment of Cancer (EORTC) and 2005 WHO-EORTC classifications of cutaneous lymphomas.[2,3] In addition, due to its remarkably indolent behavior, its status has been downregulated to that of a lymphoproliferative disorder, reflected in the new name of primary cutaneous marginal zone lymphoproliferative disorder (PCMZLPD). Thus, there are now 3 subtypes of primary cutaneous B-cell lymphoma/lymphoproliferative disorder. The diagnostic criteria for the 2 other subtypes, PCFCL and PCDLBCL-LT remain largely unchanged from the revised fourth edition of the WHO classification, although advances have been made in our understanding of these entities.

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Lecture fee from Takeda for talk on CD30 expression in cutaneous lymphoma delivered at European Association for Haematopathology Biennial Congress, September 2024.

The author has no funding or conflicts of interest to disclose.

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DOI: 10.1097/PAP.0000000000000487

TABLE 1. Primary Cutaneous Lymphomas Recognized by the International Consensus Classification*

Lymphoproliferative disorders: neoplastic but uniformly indolent and nonlife-threatening lymphoid proliferations	PCL with favorable outcome: usually low-grade clinical behavior but the potential to progress/behave in a more aggressive fashion	PCL with poor outcome: aggressive lymphomas from the outset, often with fatal outcome
Primary cutaneous marginal zone LPD	Primary cutaneous follicle center lymphoma	Primary cutaneous diffuse large B-cell lymphoma
Primary cutaneous CD4-positive small/medium T-LPD	Mycosis fungoides early stage	Primary cutaneous CD8-positive aggressive epidermotropic cytotoxic T-cell lymphoma
Primary cutaneous acral CD8-positive T-LPD	Primary cutaneous anaplastic large cell lymphoma	Primary cutaneous γ/δ T-cell lymphoma
Lymphomatoid papulosis	Subcutaneous panniculitis-like T-cell lymphoma (uncomplicated)	Subcutaneous panniculitis-like T-cell lymphoma with HLH

*Sézary syndrome is included as a primary cutaneous lymphoma but is not listed in this table.
HLH indicates hemophagocytic lymphohistiocytosis; LPD, lymphoproliferative disorder; PCL, primary cutaneous lymphoma.

Primary Cutaneous Marginal Zone Lymphoproliferative Disorder

Primary cutaneous marginal zone lymphoproliferative disorder (PCMZLPD) is typically a disease of adults with a median age at presentation of around 50 years, although the age range is broad and includes pediatric cases.[4] Patients present with solitary or localized clusters of red/brown or violaceous plaques or nodules, usually on the trunk or upper extremities. Two histologic subtypes are recognized, a class switched variant and an IgM-positive subtype.

Class switched PCMZLPD is the most commonly encountered type (80% to 90%). It involves the dermis and often subcutaneous fat with a nodular pattern of growth. Much of the infiltrate is reactive in nature. Lymphoid follicles, often with reactive germinal centers, are ubiquitous and surrounded by a predominance of small reactive T-cells which create a Th2 microenvironment.[5–7] Neoplastic cells are often in the minority. The vast majority show marked plasmacytic differentiation with the formation of plasma cell aggregates beneath the epidermis and around the peripheries of the infiltrate (Fig. 1A). Light chain restriction is easily demonstrated and is a key to making the diagnosis, in particular differentiating PCMZLPD from cutaneous lymphoid hyperplasia rich in B-cells. The majority of cases express IgG, often of the IgG4 subtype (40%), with a minority expressing IgA.[8,9] In IgM-positive PCMZLPD, neoplastic lymphocytes are usually in the majority, often with monocytoid morphology, display a diffuse growth pattern, and more frequently involve subcutis (Fig. 1B, C). Plasmacytic differentiation may be seen but is less prominent than in class switched PCMZLPD. Remnants of reactive follicles can be demonstrated but usually these are overrun by the neoplastic lymphocytes. Small reactive T-cells are present in the background but few in number and generate a Th1-type microenvironment.[5–7] In both types of PCMZLPD the neoplastic B-cells display an indeterminate phenotype, positive for CD20 and other B-cell markers along with BCL2 but typically negative for CD5, CD10, CD23, BCL6, and cyclin D1. IRTA1 and CXCR3 are usually expressed by the neoplastic B-cells in IgM positive PCMZLPD but not the class switched variant.[5]

Although chromosomal rearrangements have been reported in PCMZLPD, most frequently juxtaposing *MALT1* with *IGH*, these are seen in only a minority of cases and FISH studies do not form part of the routine diagnostic process.[10,11] Conversely, mutations of the *FAS* gene are reported in a high percentage of PCMZLPD (>60%) but not in extranodal marginal zone lymphomas arising at other sites, emphasizing the distinct nature of PCMZLPD. FAS mutations are found in both IgM positive and class switched PCMZLPD and rare patients with clonally related IgM positive and class switched PCMZLPD have been documented, precluding complete separation of these 2 subtypes on the basis of current knowledge.[5,12]

Staging should be undertaken to exclude secondary involvement of skin by other types of marginal zone lymphoma and treatment is locally directed (radiotherapy and/or excision) in the first instance. Despite relatively

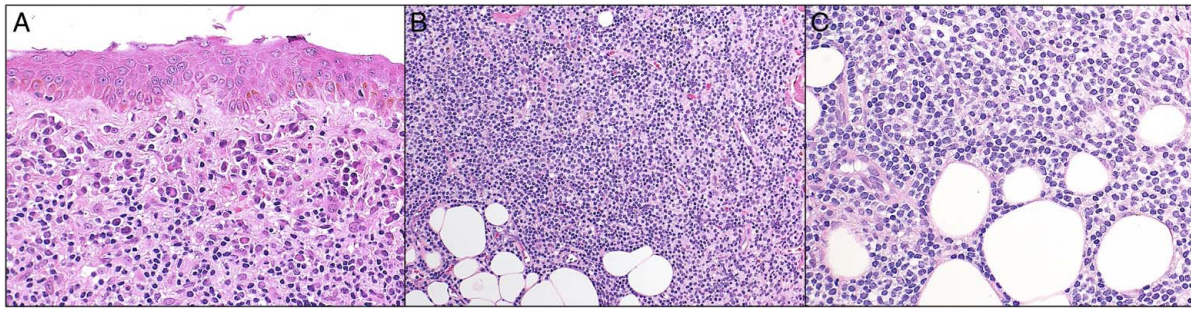

FIGURE 1. A, Neoplastic plasma cells are seen in a subepidermal location in this "class switched" primary cutaneous marginal zone lymphoproliferative disorder (PCMZLPD). B, An IgM-positive PCMZLPD showing a diffuse pattern of growth and infiltration of subcutaneous fat. C, Many of the cells display monocytoid morphology.

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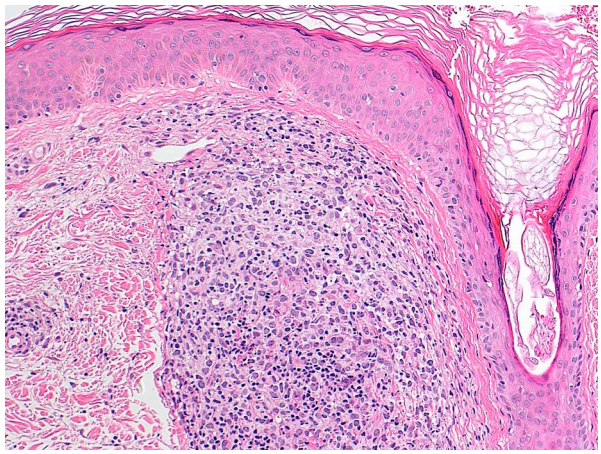

FIGURE 2. A case of primary cutaneous follicle center lymphoma with a follicular pattern of growth. The neoplastic follicles are populated by a predominance of centrocyte-like cells. Please see this image in color online.

frequent recurrence, the outcome is excellent with 100% 5-year disease specific survivals quoted in some series, hence its new designation as a lymphoproliferative disorder.[13–16]

Primary Cutaneous Follicle Center Lymphoma

Adults are most commonly affected and typically present with localized plaques, nodules, or tumors, usually on the trunk or in the head and neck region, especially the scalp. Variably well formed, but often irregular and indistinct follicles (Fig. 2), are present in some cases while others have a purely diffuse pattern of growth. The majority of neoplastic cells resemble centrocytes and are often of intermediate to large size (Figs. 2, 3A). Centroblasts may also be seen but are in the minority and never form confluent sheets.[2,3] In a small percentage of cases the centrocytes assume a spindled configuration, imparting a sarcomatoid appearance on the infiltrate.[17,18] The tumor cells express B-cell antigens and BCL6 together with other germinal center markers (eg, stathmin, MEF2B, LMO2, and HGAL), although CD10 may be weak or negative, particularly when growth is diffuse.[19–22] Staining for CD5, CD23, IRF4/MUM1, and Cyclin D1 is usually negative although rare cases express CD30.[23] BCL2 expression is variable. Weak, often only partial staining is seen in the majority of PCFCL, but in some cases, the neoplastic lymphocytes are entirely negative. Rare cases show a strong positive staining pattern.[24,25]

BCL2 gene rearrangement (*BCL2R*) can be found, but at a much lower incidence than encountered in node-based follicular lymphoma (nFL) (10% vs. 90%).[21,26] In common with nFL, PCFCL frequently harbor deletions of 1p36/*TNFRSF14*, although loss of 1p36 and *BCL2R* appear to be mutually exclusive in PCFCL whereas they are often concurrent in nFL.[21,22,27] The mutational profile of PCFCL overlaps with that in nFL in some respects, but in others is quite different. Mutations of *TNFRSF14* are present at similar frequency in both entities (30% to 40%) but in PCFCL there is a much lower incidence of mutations in chromatin modifiers (*CREBBP, KMT2D*, and *EZH2*) and *BCL2*, and a higher incidence of mutations in *TNFAIP3*.[21] Thus, the mutational profile of PCFCL shows some overlap with other subtypes of FL lacking *BCL2R*, particularly those arising at other extranodal sites.[21,28,29]

A scoring system to facilitate differentiating PCFCL from secondary cutaneous involvement by nFL, based on mutations in *CREBBP, KMT2D, EZH2,* and *EP300*, *BCL2* rearrangement and the Ki-67 index, has recently been proposed but formal staging of patients with suspected PCFCL remains essential to exclude secondary involvement by nFL.[15,26,30] First line treatment is local radiotherapy and/or excision with the majority of patients achieving complete remission.[13–15] Relapse is not infrequent but extracutaneous spread is rare (10%). The outcome is generally excellent with 5-year overall survival quoted at 87% and 5-year disease specific survival 95%, even for lymphomas with a diffuse growth pattern and large cell morphology managed by locally directed therapy alone.[13–15] Consequently, distinction from primary cutaneous diffuse large B-cell lymphoma, leg type, is paramount (see below).

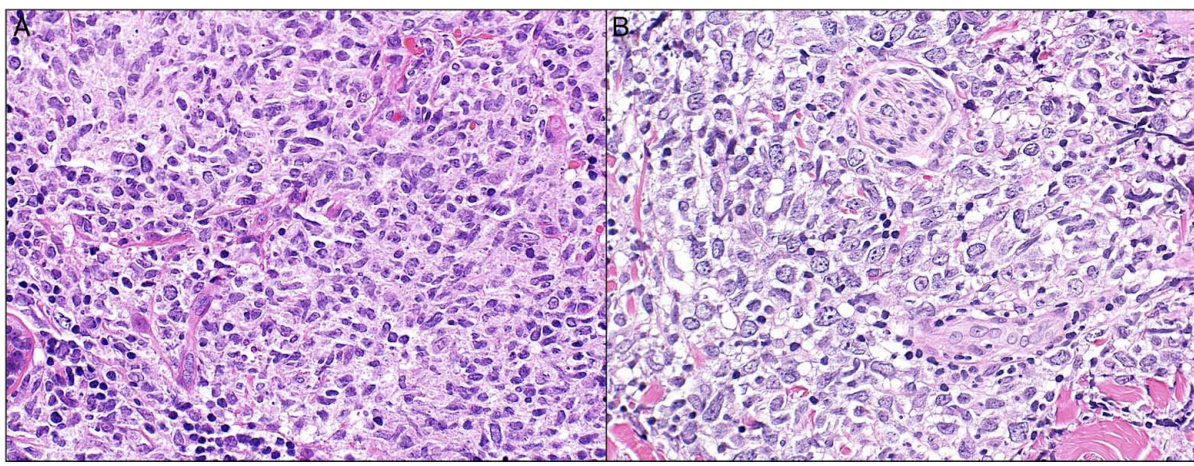

FIGURE 3. A, A case of primary cutaneous follicle center lymphoma (PCFCL) with a diffuse pattern of growth. Even though the tumor cells are of large size, they are predominantly centrocyte-like, possessing slightly elongated, angulated, or cleaved nuclei and relatively indistinct nucleoli. B, In contrast to PCFCL, the neoplastic cells in primary cutaneous diffuse large B-cell lymphoma have more rounded nuclear contours and more prominent nucleoli, resembling centroblasts and/or immunoblasts. Please see this image in color online.

Primary Cutaneous Diffuse Large B-Cell Lymphoma, Leg Type

Primary cutaneous diffuse large B-cell lymphoma, leg type (PCDLBCL-LT) is an aggressive lymphoma that occurs most frequently, but not exclusively, on the leg (10% to 15% of cases arise on the upper body). Involvement of the lower leg is most common and patients present with nodules and tumors that may ulcerate. It is typically a disease of the elderly with marked female predominance.[13,14,31–33] Biopsy shows diffuse sheets of centroblast-like and/or immunoblast-like B-cells that often fill the dermis (Fig. 3B). Expression of B-cell antigens such as CD20 and CD79a is the norm. A nongerminal center phenotype is encountered in the majority, most cases lacking CD10 but positive for IRF4/MUM1, BCL6 and BCL2, the latter usually strong and uniform.[13,25,33] However, rare cases showing typical clinical and morphologic features of PCDLBCL-LT show weak CD10 expression and/or absence of IRF4/MUM1 and/or BCL2.[13,31,34,35] In addition, while early gene expression profiling studies classified all PCDLBCL-LT as activated B-cell type and all PCFCL as having a germinal center B-cell profile, more recent investigations failed to demonstrate such a close correlation between cell of origin and PCDLBCL-LT, although the association between PCFCL and germinal center origin held up.[34,36] Cases with discrepant phenotype but otherwise characteristic features are currently accepted under the heading of PCDLBCL-LT, although it may be prudent to seek additional phenotypic or molecular support for such a diagnosis (see below). A small minority of cases show partial expression of CD30 and rare TdT positive cases have also been reported.[31,37,38] The latter raises a diagnostic dilemma with B-lymphoblastic leukemia/lymphoma, which may also present in the skin.[37,38] Absent or weak expression of CD20 is a clue to the latter.

MYC rearrangement is present in a proportion of cases but BCL2 translocations are not found, although amplification of *BCL2* and deletion of 9p21.3 harboring *CDKN2A* is common.[14,34,39] Cases with both *MYC* and *BCL2* rearrangements presenting in the skin are better classified as high-grade B-cell lymphoma (HGBCL) with *MYC* and *BCL2* rearrangement. *BCL6* rearrangements may be found.[40–42] The mutational profile of PCDLBCL-LT is distinct from other cutaneous B-cell lymphomas but overlaps significantly with that of primary CNS, primary testicular DLBCL, intravascular large B-cell lymphoma, and the MCD/C5 group of DLBCL. Of particular therapeutic and diagnostic relevance is the high frequency of *MYD88* and *CD79B* mutations.[34,43–45] In addition, 70% of cases harbor *PIM1* mutations with *MYC* mutations found in 20%.[36,43]

PCDLBCL-LT is an aggressive lymphoma that requires treatment with systemic multiagent chemotherapy with or without targeted radiotherapy.[14,15] Outcomes remain poor with 5-year disease-specific survival in the region of 60% to 70%, although more novel approaches targeting B-cell receptor signaling and NFκB pathways with Ibrutinib or Lenalidomide offer hope for the future (Table 2).[46,47] It is therefore extremely important to differentiate PCDLBCL-LT from PCFCL with diffuse growth and large cell morphology in view of their markedly different clinical behavior and treatment requirements.[14,25] Standard immunophenotyping may not always be conclusive and distinction may rely on the cytologic appearance of the neoplastic cells (Fig. 3). Given that differentiating large centrocytes from centroblasts may not be straightforward or reproducible, further studies may be warranted in equivocal cases. Positive staining for FOXP1 and IgM is highly predictive for PCDLBCL-LT, as is a demonstration of an *MYD88* mutation, which can relatively easily be demonstrated with a single gene assay.[31,48,49]

PRIMARY CUTANEOUS T-CELL LYMPHOMA

Certain subtypes of primary cutaneous T-cell lymphomas display significant pathologic overlap, rendering distinction on the basis of pathologic features extremely difficult, and sometimes impossible. This is especially true for those entities that display prominent epidermotropism and, often, a cytotoxic phenotype. These lymphomas display markedly different clinical behavior and outcomes, ranging from spontaneous resolution to rapid, often fatal, progression. Although pathology can provide diagnostic

TABLE 2. Potential Therapeutic Targeting of Signaling Pathways Altered by Molecular/Genetic Alterations In Primary Cutaneous Lymphoma

PCL with favorable outcome	PCL with poor outcome	Targetable pathways/abnormalities	Potential therapeutic agents
	PCDLBCL-LT	BCR signaling pathway	Ibrutinib
Early stage MF	Advanced stage MF	JAK/STAT pathway miR-155	Ruxolitinib
		chromatin modification	cobomarsen (MRG-105)
			histone deacetylase inhibitors
	pcAECTL	JAK/STAT pathway	Ruxolitinib
		chromatin modification	histone deacetylase inhibitors
	pcGDTCL	JAK/STAT pathway	Ruxolitinib
		MAPK pathway	various, for example, BRAF and MEK inhibitors
		chromatin modification	histone deacetylase inhibitors
SPTCL (uncomplicated; HAVCR2 wild type)	SPTCL with HLH (HAVCR2 mutated)	JAK/STAT pathway	Ruxolitinib
		TNFα through NFκB pathway	multiple, for example, mutiple, for example, temsirolimus, everolimus, idelalisib
		MTOR signaling	

HLH indicates hemophagocytic lymphohistiocytosis; MF, mycosis fungoides; pcAECTL, primary cutaneous CD8 positive aggressive epidermotropic cytotoxic T-cell lymphoma; PCDLBCL-LT, primary cutaneous diffuse large B-cell lymphoma, leg type; pcGDTCL, primary cutaneous γ/δ T-cell lymphoma; PCL, primary cutaneous lymphoma; SPTCL, subcutaneous panniculitis-like T-cell lymphoma.

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TABLE 3. Differential Diagnosis of Epidermotropic Primary Cutaneous Lymphomas and Lymphoproliferative Disorders

Epidermotropic T-cell lymphoma/LPDs with cytotoxic phenotype	Pathologic clues, additional and comment	Typical clinical presentation and course	Standard first line therapy	5-year survival DSS*, n (%)
Mycosis fungoides	Phenotype can be CD4+, CD8+, or γ/δ. Some cases express CD30 in variable numbers of cells; usually a low percentage in early stage, higher proportion in late stage and/or large cell transformation	Slowly evolving patches and plaques. CD8-positive cases associated with young age and/or hypopigmentation	Skin directed therapies for early stage disease, for example, topical steroid, retinoids, phototherapy	88
Pagetoid reticulosis	Epidermal hyperplasia and hyperkeratosis. Neoplastic lymphocytes confined to epidermis, colonize lower half. Approximately 50% of cases express CD8+ and/or CD30	Solitary plaque at the acral site	Excision and/or radiotherapy	100
LyP type-D	CD8 positive, CD30 positive	Ulcerating papules. Spontaneous resolution	No treatment, excellent prognosis	100
LyP with DUSP22-R	Biphasic morphology and pattern of CD30 expression	Ulcerating papules. Spontaneous resolution	No treatment, excellent prognosis	100
pcAECTL	CD8 positive, CD30 negative. Retention of CD7 with loss of other T-cell antigens	Multiple ulcers and tumors. Rapid progression from outset	Systemic polychemotherapy	18
pcGDTCL	γ/δ phenotype, CD4-/CD8-, CD56+, preferential loss of CD5	Ulcerating nodules and tumors, plaques. Rapid progression from outset	Systemic polychemotherapy +/- bone marrow transplant	NR

*Survival figures quoted from: Willemze R. et al 2005[3] (reference 3).

DSS indicates disease-specific survival; DUSP22-R, DUSP22-R rearrangement; LPD, lymphoproliferative disorder; LyP, lymphomatoid papulosis; NR, not reached; pcAECTL, primary cutaneous CD8 positive aggressive epidermotropic cytotoxic T-cell lymphoma; pcGDTCL, primary cutaneous γ/δ T-cell lymphoma.

clues, reliable separation of these entities can only be achieved on the basis of clinical features, predominantly the number, type, and distribution of lesions and rapidity of growth at presentation and shortly thereafter. Thus, correlating the pathologic findings with clinical features remains an integral part of the diagnostic process in the ICC[50] (Table 3). Since the revised fourth edition of the WHO classification, there has been only one significant change in the nomenclature of primary cutaneous lymphomas, primary cutaneous acral CD8 positive T-cell lymphoma being reclassified as an LPD.[16] Nevertheless, new molecular and cytogenetic data has been accumulated for a variety of cutaneous T-cell lymphomas that is of biological and, in some instances, clinical and therapeutic relevance.

Mycosis Fungoides and Variants

A detailed discussion of mycosis fungoides (MF) and Sézary syndrome is beyond the focus of this article, and this section will focus of the pathology of MF and some of its variants, highlighting features that are important in establishing a diagnosis. MF is the most frequently encountered type of cutaneous T-cell lymphoma, and should be considered a separate entity from Sézary syndrome. Problems in arriving at a diagnosis begin with clinical examination. The classic presentation is with patches and plaques, but a large variety of nontypical manifestations, many resembling inflammatory dermatoses, have been described.[51] In biopsies of patch or early plaque stage lesions, diagnostic problems are compounded by the frequent presence of histologic changes more commonly seen in benign dermatoses, including spongiosis, psoriasiform hyperplasia, and interface dermatitis-like changes.[52] Variants of MF recognized in the ICC are folliculotropic mycosis fungoides (FMF), Pagetoid reticulosis (PR), and granulomatous slack skin (GSS).[30] In FMF, there are patches, plaques, or grouped papules with a predilection for head and neck skin. Secondary acneiform lesions, alopecia, and pruritis are common. PR is a rarely encountered variant of MF in which patients present with a solitary erythematous lesion, usually on the hands or feet, that slowly evolves into a thick, often verruciform plaque. GSS affects young adults and manifests as large pendulous skin folds in the axillary or inguinal regions. It is exceedingly rare and will not be discussed further.

Many of the histologic features seen in MF, particularly early stages, are nonspecific. This often includes a high proportion of small reactive lymphocytes in the papillary dermis. Focus should therefore be on intraepidermal lymphocytes and identifying changes most predictive of a neoplastic process.[53] The neoplastic cells in MF have highly irregular hyperchromatic nuclei (cerebriform cells). These may be small in the early stages of the disease but are of medium to large size in established MF. The presence of medium-large cerebriform cells within the epidermis is a strong feature in support of the diagnosis as is the presence of long linear arrays of lymphocytes at the dermo-epidermal junction ("lymphocyte tagging"), a degree of epidermotropism disproportionate to any spongiosis which might be present and Pautrier's microabscesses[53,54] (Fig. 4). In FMF the intraepithelial lymphocytes show preferential infiltration of hair follicle epithelium and may be associated with secondary follicular mucinosis. There are commonly inflammatory changes in the surrounding dermis due to infection

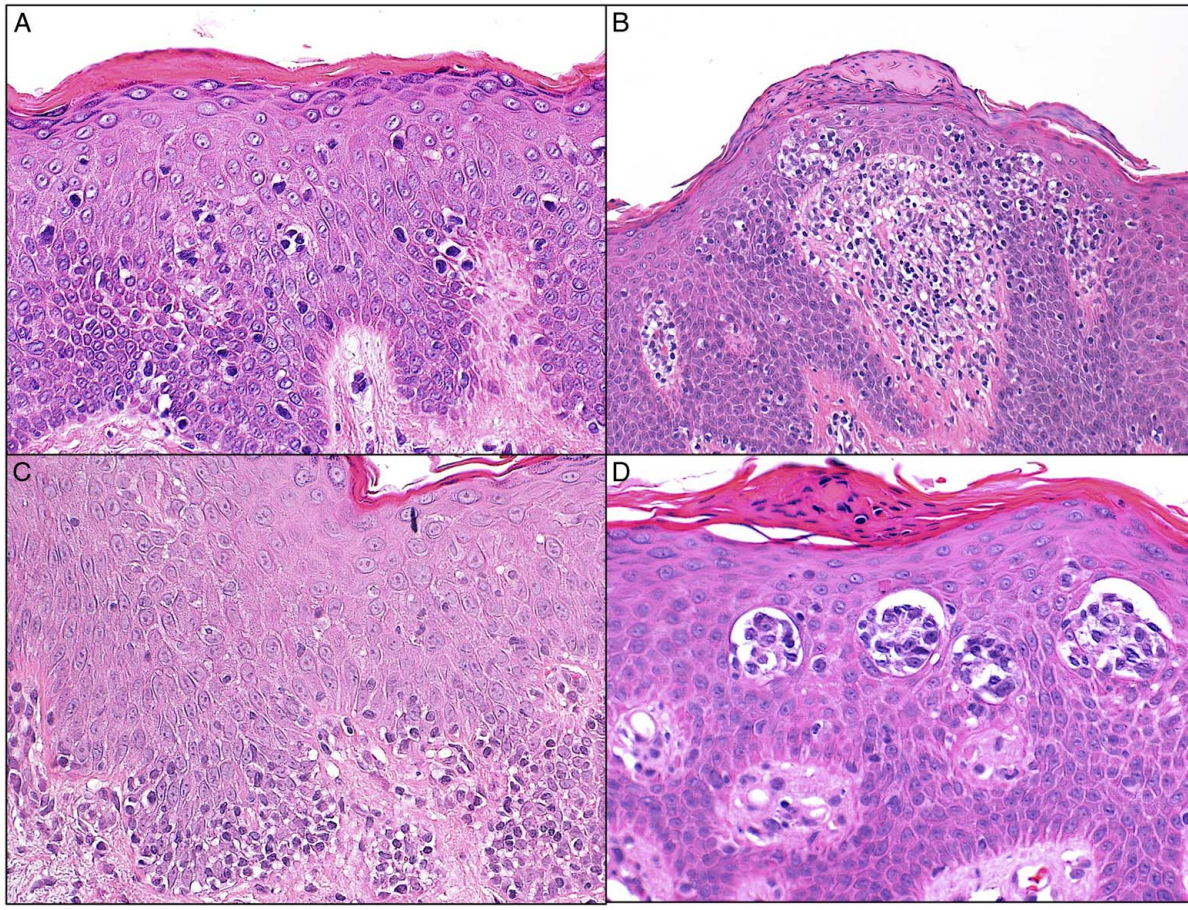

FIGURE 4. Positive features in support of a diagnosis of mycosis fungoides. A, Medium-large cerebriform cells in the epidermis. Irregular hyperchromatic nuclei are at least the size of nuclei in basal keratinocytes and larger than the nuclei of dermal lymphocytes. B, Disproportionate degree of epidermotropism. C, Linear arrays of lymphocytes alongside basal keratinocytes ("lymphocyte tagging"). D, Pautrier's microabscesses. Discrete intraepidermal collections of neoplastic lymphocytes. Please see this image in color online.

and rupture of hair follicles.[53,54] The intraepidermal lymphocytes in PR are confined to the epidermis and associated with prominent psoriasiform hyperplasia and parakeratosis (Fig. 5). They are often surrounded by a halo of clear cytoplasm. The degree of epidermotropism is striking with colonization of the entire lower half of the epidermis common

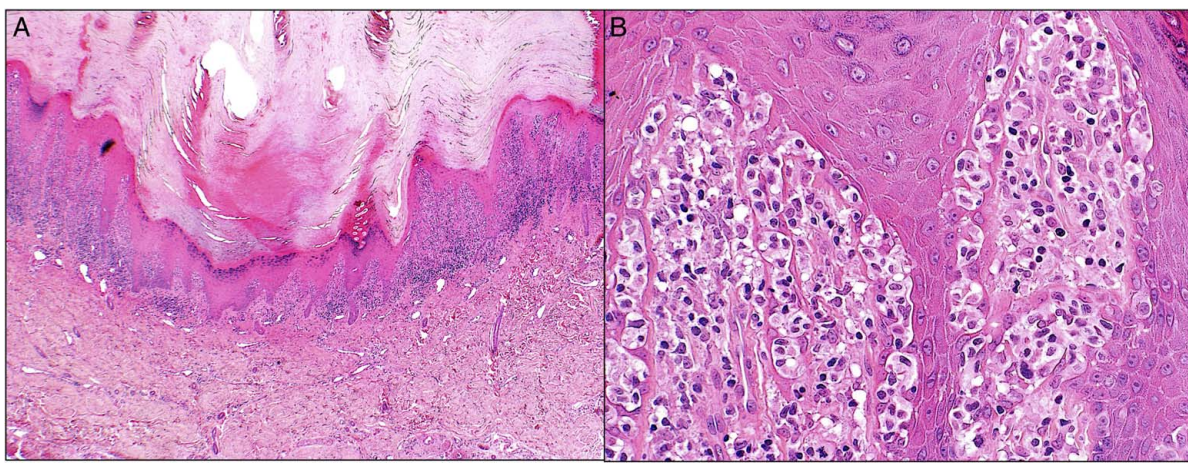

FIGURE 5. Pagetoid reticulosis. A, There is usually marked hyperkeratosis and prominent epidermal hyperplasia. B, There is striking epidermotropism. The neoplastic lymphoid cells are large with perinuclear halos, and largely confined to the lower half of the epidermis. Please see this image in color online.

(Fig. 5). Pautrier's microabscesses are rare in this form of the disease.[53,54]

In MF and FMF, the neoplastic lymphocytes are typically CD3/CD4-positive T-cells of α/β type (TCR-βF1 positive).[53,54] There may be loss of T-cell-associated antigens, particularly CD7, but often only prominent in later stages of the disease. In order to be significant, CD7 loss should be almost complete (ie, close to 100% of presumed tumor cells), as there may be partial loss of CD7 in inflammatory dermatosis.[55] Neoplastic T-cells often show strong expression of PD1 but CD10 and CXCL13 are usually negative. CD30 may be expressed. When present in early-stage disease, only a minority of cells are positive, but it is seen more frequently in advanced disease and is common following large cell transformation. Rare phenotypic variants include CD8-positive cases (often in younger patients and associated with hypopigmentation) and/or TCR-γ/δ positive cases. To qualify as MF, such cases must present with typical slow growing patches and plaques. The neoplastic cells in PR are frequently CD8 positive and often also express CD30, although CD4 positive and CD4/CD8 negative phenotypes may be seen.[56]

Clonality studies should be interpreted with caution in MF. There is a high false negative rate in early-stage lesions.[57] False positive results are also possible as dominant T-cell clones are not infrequently demonstrated in benign dermatoses.[58] In practice clonality assays should be avoided when only a single biopsy is available and there is doubt as to the neoplastic nature of the infiltrate after pathologic examination. Assessment of clonality should be reserved for when material from multiple lesions is available, the presence of the same clone at 2 or more sites being highly predictive of neoplasia.[59] Detailed analysis of transcriptional and genetic changes in MF have identified alterations to signaling pathways and epigenetic mechanisms in MF that may be amenable to targeted therapy. Implicated pathways include JAK-STAT signaling secondary to reduced SOCS1 expression as a consequence of deletions, unbalanced translocations, upregulation of miR-155 which targets SOCS1 mRNA, or methylation of the SOCS1 promoter.[60–62] Mutations of *DNMT3A, TET2,* and *IDH2* have also been reported.[61,62]

The clinical course is of MF is generally indolent but, in some patients, there is progression to tumors and/or erythroderma, and rarely, extracutaneous dissemination. The stage of disease, as determined by the International Society for Cutaneous Lymphomas and the European Organization for Research and Staging System, predicts the outcome and dictates the therapeutic approach. Outcome in early stage disease (stages I and IIA) is generally excellent but is significantly poorer for stage IIB and above.[63,64] In general, the outcome for FMF is poorer than for classic MF, particularly when patients present with advanced disease characterized by thick plaques and a dense and deep perifollicular lymphoid infiltrate.[65] PR is an indolent disease that responds well to surgical excision radiotherapy with excellent outcomes.[66]

Making a diagnosis of MF in its early stages can be problematic and can take several biopsies of a period of months to years.[67] It should also be remembered that not every epidermotropic T-cell lymphoma represents MF, and care should always be taken to ensure one is not dealing with other types of cutaneous lymphoma. As will be discussed under various headings below, this applies particularly to epidermotropic lymphomas and lymphoproliferative disorders with a cytotoxic phenotype in which similar and often overlapping pathologic features display a very broad clinical spectrum with vastly differing outcomes and radically different approaches to treatment (Table 3).

Primary Cutaneous CD30-Positive T-cell Lymphoproliferative Disorders

Primary cutaneous CD30-positive T-cell lymphoproliferative disorders encompass a spectrum of disease with overlapping histologic, immunophenotypic, and genetic features. Lymphomatoid papulosis (LyP) lies at one end of the spectrum and primary cutaneous anaplastic large cell lymphoma (pcALCL) at the other.

Lymphomatoid Papulosis

A diagnosis of LyP is dependent on correlating an appropriate histologic appearance with a characteristic clinical presentation and course, principally the tendency of lesions to spontaneously resolve. The typical presentation is with crops of papules and nodules, that develop, become hemorrhagic, ulcerate over 3 to 4 weeks, and then undergo resolution. Resolution may take up to 12 weeks and leave varioliform scars. Lesions may be few and localized or number in the hundreds with widespread distribution.[68] In a small subset of patients with angioinvasive growth (see below) papules evolve and ulcerate, forming large eschar-like ulcers before spontaneously healing, usually with prominent scarring.[69] The age range is broad and LyP is well documented in children.[70] It is important to note that around 10% to 20% of patients with LyP will also develop clonally related mycosis fungoides, concurrent with, before, or subsequent to a diagnosis of LyP.[70] This can create problems for the pathologist in differentiating LyP from large cell transformation of MF.

The morphologic appearance of LyP is diverse and 6 histologic variants have been described: LyP types A, B, C, D, and E, and DUSP22 rearranged LyP.[53,54] LyP types A and C are the prototypic form of the disease characterized by large CD30-positive T-cells with anaplastic morphology set in a mixed inflammatory cell background.[71] In type A LyP, CD30-positive cells constitute a minority of cells scattered among small lymphocytes, histiocytes, plasma cells, neutrophils, and/or eosinophils, whereas in type C LyP they form aggregates and/or sheets and account for > 50% of the infiltrate. Two types of epidermotropic LyP are recognized. In LyP type B the epidermotropic cells are CD4-positive, and lesions resemble those of mycosis fungoides, whereas in LyP type D the neoplastic cells express CD8 (Fig. 6).[71,72] LyP type E is characterized by angiocentric and angioinvasive growth resulting in wedge-shaped necrosis of the overlying dermis and epidermis, clinically manifesting as eschar-like ulcers (Fig. 7).[69] The final LyP variant is defined by the presence of DUSP22 rearrangement and a characteristic biphasic morphology, a prominent epidermotropic component of small to medium-sized lymphocytes that weakly express CD30, overlying nodular aggregates of large lymphoid cells that are strongly positive for CD30 (Fig. 8).[73]

The neoplastic lymphocytes in LyP types A and C show uniform strong expression of CD30 and usually express CD4 along with cytotoxic molecules. Rare cases, mostly in pediatric patients, are CD8 positive. One or more of the pan-T-cell antigens CD2, CD3, CD5, and CD7 are frequently lost. IRF4/MUM1 is expressed in the majority

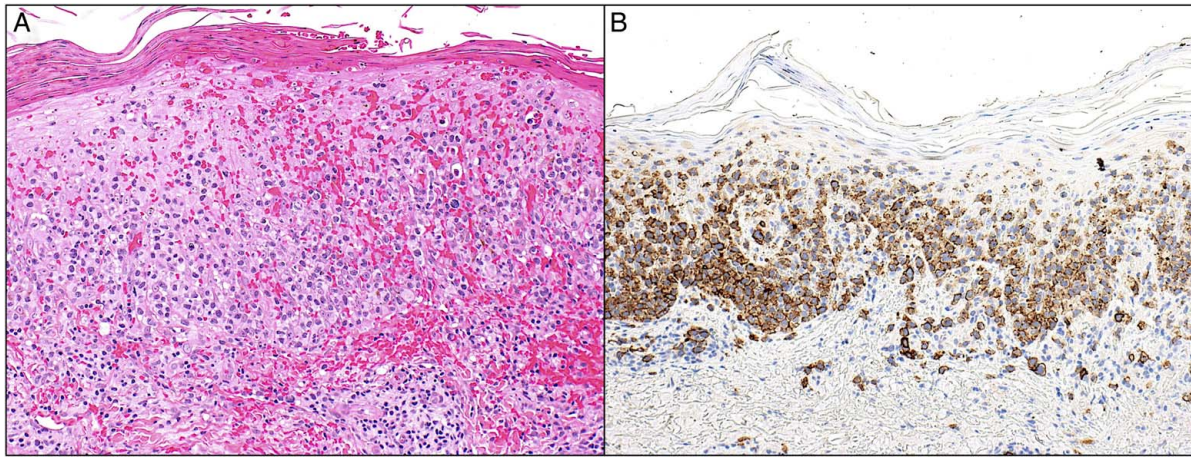

FIGURE 6. Lymphomatoid papulosis type D. A, Prominent epidermotropism is seen. B, The neoplastic lymphocytes express CD30. This can help to distinguish lymphomatoid papulosis type D from primary cutaneous CD8-positive aggressive epidermotropic cytotoxic T-cell lymphoma. Please see this image in color online.

but staining for ALK is negative.[74,75] In type B LyP, the epidermotropic lymphocytes are also CD4 positive although CD30 expression is reported to be variable.[71] Expression of CD8 and CD30 is the norm in type D and type E lesions.[69,72] Cases of LyP associated with *DUSP22* rearrangement display the above-mentioned biphasic pattern of CD30 expression and can be CD4 positive, CD8 positive, or double negative for CD4 and CD8.[73] T-cell receptor genes are clonally rearranged in most cases and when other lymphomas are present in the same patient (eg, MF or pcALCL), they are clonally related.[76] Mutations in epigenetic modifying genes such as *SETD2, KMT2A* and *CREBBP*, as well as in *STAT5A, DNMT3A* and *PLCG1,* have been documented and rearrangements involving *TYK2* or *JAK2* have also been reported.[77,78]

LyP lesions resolve spontaneously and the prognosis is excellent for all subtypes, although long-term follow-up is recommended in view of the association with other lymphoma subtypes.

Primary Cutaneous Anaplastic Large Cell Lymphoma

The majority of patients (80%) with pcALCL present with solitary or localized, often erythematous, nodules or tumors, most frequently involving the extremities.[70] In some instances, the tumor cells incite florid pseudoepitheliomatous hyperplasia that may clinically and pathologically mimic squamoproliferative lesions such as keratoacanthoma or squamous cell carcinoma (Fig. 9). The majority of patients are adult (median age = 60 y) with only rare pediatric cases reported.[70]

In most cases, the tumor cells are large with abundant cytoplasm, pleomorphic nuclei, finely dispersed chromatin, and prominent nucleoli. Immunoblast-like morphology is less frequently encountered but acceptable for the diagnosis provided other criteria, particularly uniform CD30 expression and localization to the skin, are fulfilled. The tumor cells form nodules or sheets within the dermis and may extend into subcutaneous fat. Angioinvasion, intralymphatic spread, and epidermotropism are occasionally

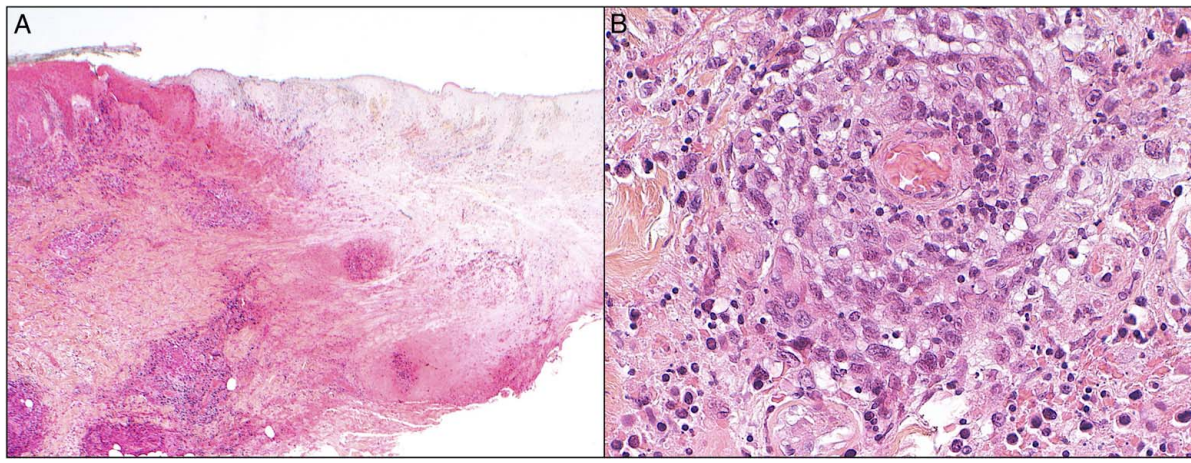

FIGURE 7. Lymphomatoid papulosis type E. A, An incisional biopsy from the edge of an eschar-like ulcer showing part of a wedge-shaped dermal infarct. Vessels feeding the infarcted area are surrounded by a lymphoid infiltrate. B, Higher power view of an affected vessels showing infiltration by large lymphoid cells with anaplastic morphology. Please see this image in color online.

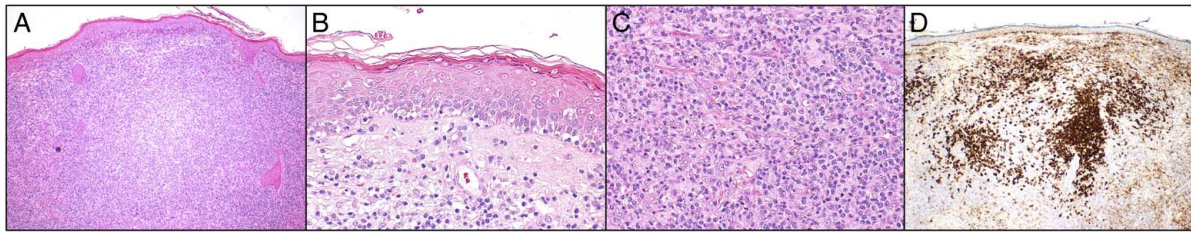

FIGURE 8. Lymphomatoid papulosis with *DUSP22* rearrangement. A, An extensive dermal infiltrate is present with changes also seen in the epidermis. B, The epidermis overlying and adjacent to the dermal infiltrate is infiltrated by small lymphocytes, in this case predominantly lining up alongside basal keratinocytes. C, Compared with the intraepidermal lymphocytes, those in the dermis are much larger and form ill-defined nodules. D, Staining for CD30 shows a strong positive reaction within the population of large dermal lymphoid cells but weaker expression by the smaller epidermotropic T-cells. Please see this image in color online.

seen.[79,80] A proportion of cases harbor *DUSP22* rearrangement may show a similar biphasic morphology to that described for *DUSP22* rearranged LyP (see above), although others are indistinguishable from pcALCL without the translocation.[81] Mixed inflammatory cells, including small lymphocytes, histiocytes, neutrophils and eosinophils may be present in the background and a neutrophil-rich variant has been reported.[80,82,83] Staining for ALK should be negative. Although ALK positive primary cutaneous lymphomas otherwise displaying similar clinical and pathologic features of pcALCL have been reported they remain poorly understood and should not yet be placed in this category but managed carefully with close clinical pathologic correlation.[84,85]

Prognosis in pcALCL is good in most cases with 5-years disease specific survival or 86% to 96%.[70,86] Involvement of locoregional lymph nodes does not impact adversely on outcome although lower limb involvement, particularly if extensive, is associated with poor prognosis. First line treatment is locally directed with resection and/or radiotherapy. Patients with more aggressive or recalcitrant disease can be managed with systemic chemotherapy and/or brentuximab vedotin.

Primary Cutaneous CD4-Positive Small/Medium T-Cell Lymphoproliferative Disorder

Primary cutaneous CD4-positive small/medium T-cell lymphoproliferative disorder (pc SMTLPD) is fully recognized in the ICC having previously been regarded a provisional entity in the revised fourth edition of the WHO classification.[16,50] A diagnosis of pcSMTLPD should be restricted to solitary nodules or plaques that most frequently arise on the head and neck or upper trunk in the absence of patches and plaques elsewhere. When the definition is limited to this clinical scenario the course is benign with 100% 5-year survival, hence, its designation as a

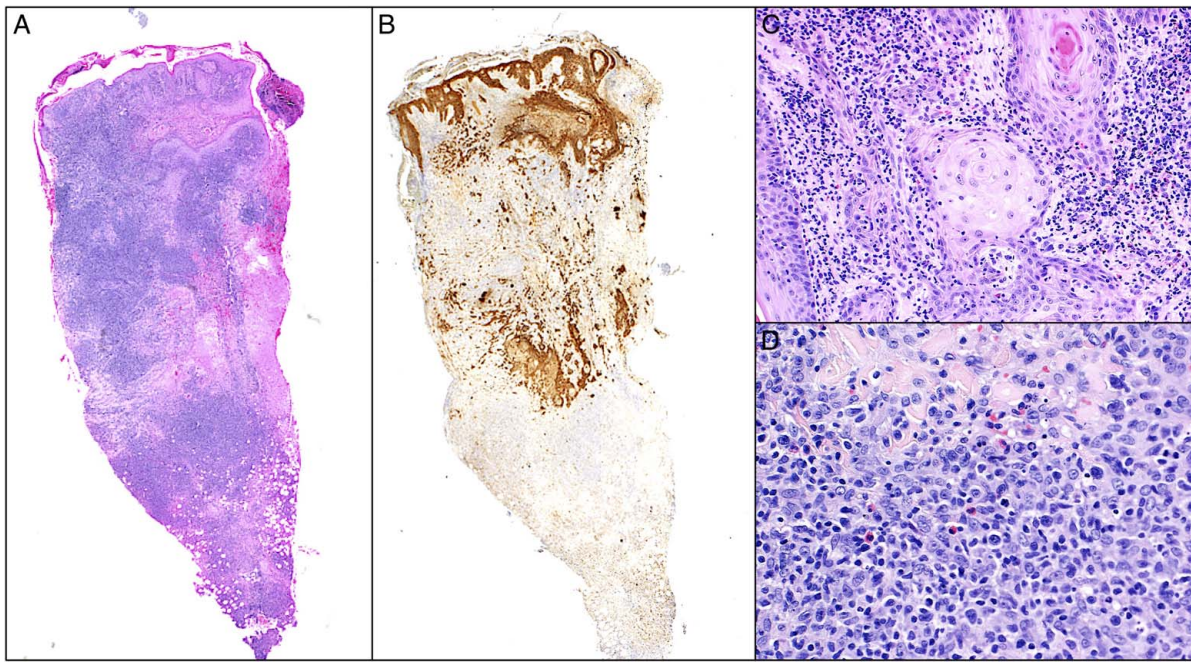

FIGURE 9. Primary cutaneous anaplastic large cell lymphoma with pseudoepitheliomatous hyperplasia. A, Lymphoid infiltrate in the dermis and subcutaneous fat associated with down-growths of epithelium originating from epidermis. B, staining for epithelial membrane antigen highlights epithelium. C, Higher power view of epithelium showing evidence of differentiation and lack of significant cytologic atypia. D, Neoplastic lymphoid cells. Please see this image in color online.

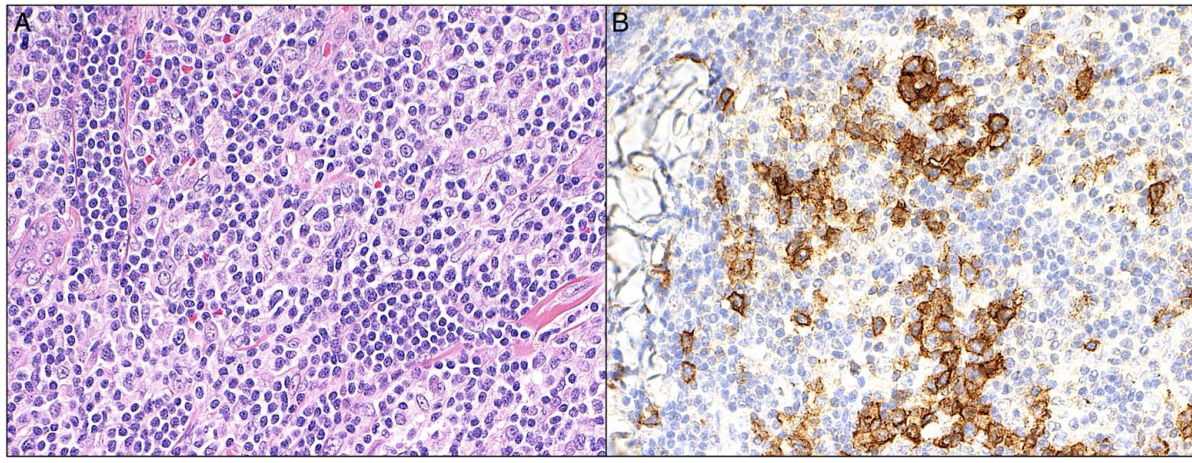

FIGURE 10. Primary cutaneous CD4-positive small/medium T-cell lymphoproliferative disorder. A, Loose aggregates of medium to large cells with irregular nuclei are seen against a background of small lymphocytes. The latter typically comprises a mixture of reactive CD4-positive and CD-8-positive T-cells, as well as B-cells. B, Staining for PD1 highlights the neoplastic lymphocytes. These are almost always in the minority. Please see this image in color online.

lymphoproliferative disorder in order to avoid unnecessary staging investigations and over-treatment.[87–91] There is considerable overlap with cases that previously would have been labeled cutaneous T-cell pseudolymphoma. Examples of CD4-positive primary cutaneous lymphoma presenting with multiple, large, rapidly growing lesions, sheets of large cells, and/or a high proliferation index have a much more aggressive clinical course and are better regarded as peripheral T-cell lymphoma, NOS.

A nodular and/or diffuse dermal infiltrate is usually present, although a minority of cases may display a superficial band-like pattern. The defining histologic feature is the presence of small clusters of intermediate to large CD4-positive T-cells that show bright expression of CD279/PD1-positive CD4-positive T-cells (Fig. 10). These comprise a minority of the infiltrate (by definition there should be $< 30\%$ large lymphoid cells), and they are set in a mixed background of reactive small CD4-positive and CD8-positive T-cells, B-lymphocytes, histiocytes and variable numbers of plasma cells, neutrophils, and eosinophils.[50,87–91] The tumor cells may show loss of CD7 but this may be difficult to discern due to the surrounding reactive T-cells. Expression of other "follicular helper T-cell antigens" such as CXCL13, ICOS, and BCL6 can be seen but CD10 is usually negative.[92] Cyclin D1 is often positive. The Ki67 should not exceed 30%.[92] Occasionally, plasma cells with light chain restriction can be seen but when germinal centers and/or light chain restricted plasma cells are present a differential diagnosis of primary cutaneous marginal zone lymphoproliferative disorder should be considered.[93] T-cell receptor genes are clonally rearranged in pcSMTLPD, and isolated somatic mutations in *DNMT3, ARID1A, EP300, SETD2, TP53, SH2B3*, and *NF1* have been described, although the mutational profile of has not been studied in depth.[93,94] Only locally directed therapy is required and often surgical excision is sufficient treatment. Survival is 100%.

It is important to distinguish pcSMTLPD from other CD4-positive T-cell lymphomas that infiltrate the skin. When there is a significantly aberrant phenotype with loss of CD2, CD3, or CD5, and/or when few reactive CD8-positive T-cells or B-cells are present in the infiltrate, a diagnosis of peripheral T-cell lymphoma, NOS should be considered.[89] Distinction should also be made with recently described cases of primary cutaneous peripheral T-cell lymphoma with a T-follicular helper phenotype. These are yet to be included in lymphoma classifications but data accumulated to date indicates that patients present with multiple lesions populated by T-cells expressing at least 2, but usually 3 of more T-follicular helper cell markers (CD10, ICOS, BCL6, CXCL13, and PD1). Systemic spread may occur and chemotherapy is generally required.[95,96]

Primary Cutaneous Acral CD8+ T-Cell Lymphoproliferative Disorder

Primary cutaneous acral CD8+ T-cell lymphoproliferative disorder was initially described as an indolent CD8-positive lymphoid proliferation on the ear, but the clinical spectrum has subsequently been expanded to reflect its distribution at other acral sites.[97–99] Included as a provisional entity in the revised fourth edition of the WHO classification under the rubric of primary cutaneous acral CD8-positive T-cell lymphoma, it is now recognized as a definite type but has been "down-graded" to a lymphoproliferative disorder in the current ICC.[16,100] Patients present with a solitary slow growing reddish/purple nodule or plaque at an acral site, most frequently on the face, particularly ear or nose, but sometimes on hands or feet. There are rare reports of bilateral lesions on the ears and feet.[97,99,101–103]

Biopsy reveals a diffuse dermal infiltrate of uniform, intermediate-size lymphoid cells with irregular nuclei, finely dispersed chromatin, and small to medium nucleoli, that spares the epidermis and adnexal structures but may extend into subcutis (Fig. 11A).[97,103] Mitotic figures are sparse and there is no angioinvasion or necrosis. By definition, the neoplastic lymphoid cells are of α/β type (TCR-βF1 positive) with a cytotoxic phenotype (CD8, TIA-1 positive). CD3 expression is the norm but one or more of CD2, CD5, and CD7 are often lacking. They are negative for CD4, CD30, CD56, CD57, TdT, and EBV. In the vast majority of cases, staining for CD68 using any of the commonly available antibodies (ie, PG-M1, KP1, and KiM1P) shows a characteristic Golgi-dot pattern which is not seen in other types of cutaneous T-cell lymphoma (Fig. 11B).[101,103] The

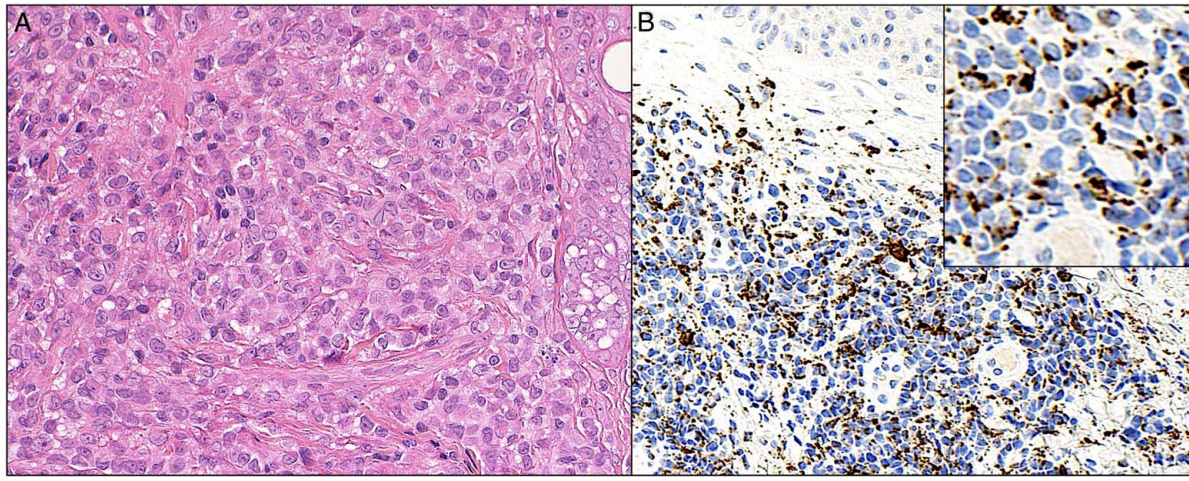

FIGURE 11. Primary cutaneous acral CD8-positive T-cell lymphoproliferative disorder. A, Typical appearance: uniform cells with finely dispersed chromatin and small nucleoli forming a diffuse infiltrate which is sparing the hair follicle in this view. B, Staining pattern with antibodies to CD68 can help distinguish primary cutaneous acral CD8-positive T-cell lymphoproliferative disorder from other types of T-cell lymphoma: a Golgi dot positive pattern is seen (inset). Please see this image in color online.

Ki67 fraction is uniformly low, usually $<10\%$. The neoplastic cells have clonal T-cell receptor gene rearrangements but little else is known about the molecular landscape of this tumor. First line treatment is surgical excision and/or local radiotherapy. Recurrences are seen in ~20% of cases but extracutaneous spread is exceptional and the prognosis is excellent.[103]

Primary Cutaneous CD8-Positive Aggressive Epidermotropic Cytotoxic T-Cell Lymphoma

Primary cutaneous CD8-positive aggressive epidermotropic cytotoxic T-cell lymphoma (pcAECTL) is a rare but very aggressive disease in adults. Patients present with a generalized, rapidly progressing eruption of patches, plaques, nodules, and ulcerating tumors without a preceding history of slowly evolving patches and plaques.[104–106] Although confined to the skin at presentation, there is typically early dissemination to other extranodal sites such as testes, lungs, spleen, and CNS.

Massive infiltration of the epidermis by cytotoxic T-cells of α/β type is the histologic hallmark of this disease. Individual tumor cells are of medium to large size with irregular, hyperchromatic of immunoblast-like nuclei. Typically, these give rise to a Pagetoid reticulosis-like pattern in the epidermis, often associated with epidermal necrosis and ulceration, and without the Pautrier's microabscesses or basal tagging of MF (Fig. 12).[104–106] Dermal infiltration is common and angioinvasion may be seen.[104–106] The neoplastic T-cells are TCR-βF1 positive, TCR-γ/δ negative, and express cytotoxic molecules (TIA-1and/or granzyme B) in addition to CD8. CD4 is negative. They are positive for CD3 and, unlike many other cutaneous T-cell lymphomas retain CD7, but CD2 and CD5 are frequently lost. Staining for CD30, CD56, and EBV is also negative.[104–106] Overactivity in the JAK2 signaling pathway is heavily implicated in the pathogenesis of this neoplasm. Rearrangements of *JAK2* or mutually exclusive deletions or loss of function mutations of negative regulators of the JAK-STAT pathway, *SH2B3* or

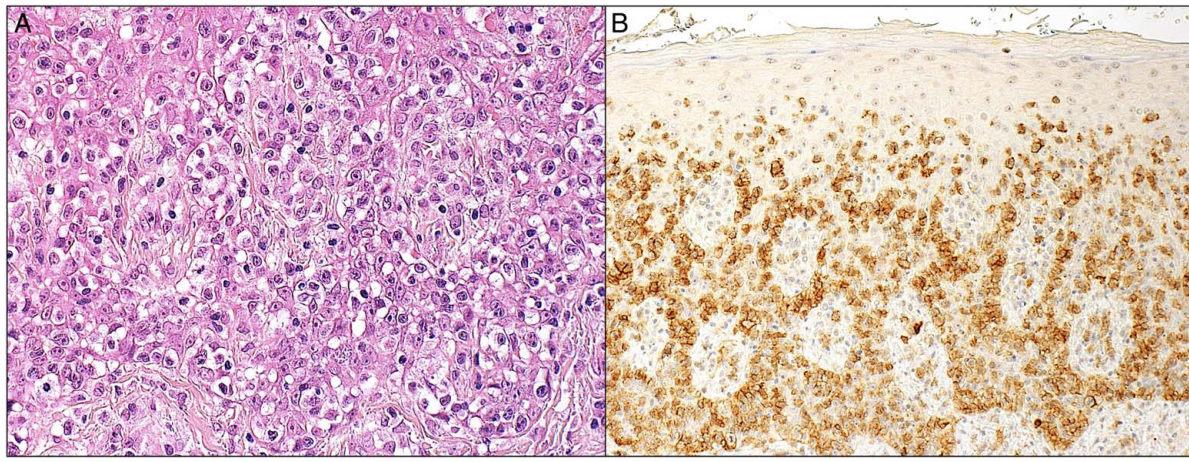

FIGURE 12. Primary cutaneous CD8-positive aggressive epidermotropic cytotoxic T-cell lymphoma. A, Prominent epidermotropism characterizes this entity. B, By definition, the neoplastic cells express CD8. Please see this image in color online.

SOCS1 are present in 3 quarters of cases 75%.[107] In addition, pathogenic activating mutations of JAK-STAT pathway genes such as *JAK3* or *STAT5B* are also common.[107] There is no standard treatment for pcAECTL. Most cases are managed with CHOP-like regimens or Gemcitabine but the outlook is extremely poor with a median survival of 12 months.[104–106]

There is significant morphologic overlap between pcAECTL and other epidermotropic T-cell proliferations with a cytotoxic phenotype, including CD8 positive variants of mycosis fungoides, some examples of pagetoid reticulosis and LyP type D. Strong expression of CD7 in the absence of other T-cell associated antigens may point to a diagnosis of pcAECTL over MF and pagetoid reticulosis, while strong expression of CD30 may favor LyP, but it is only the distinctive clinical features of these entities that allows them to be reliably distinguished (Table 3).

Subcutaneous Panniculitis-Like T-Cell Lymphoma

Subcutaneous panniculitis-like T-cell lymphoma (SPTCL) is a rare subtype of cutaneous lymphoma. The median age at presentation is 35 years but the age range is broad and 20% of cases are under 20-years old.[108,109] Twenty to forty percent of patients also have autoimmune disease, most frequently systemic lupus erythematosus, and autoantibodies are frequently present (65% of cases).[108–111] Patients present with multiple deep-seated nonulcerating nodules, usually on the trunk or limbs. Systemic symptoms, cytopenia, raised ESR and abnormal liver function tests are common, and hemophagocytic lymphohistiocytosis (HLH) occurs in 15% to 35% of patients.[108]

In pure form, SPTCL is limited to subcutaneous fat and periadnexal adipose tissue. The neoplastic lymphocytes show a lobular distribution with septal sparing. There is no involvement of dermal connective tissue or epidermis. Lymphoma cells are of small to medium size with hyperchromatic nuclei and often a rim of pale cytoplasm. They infiltrate between adipocytes diffusely and in small aggregates, and characteristically encircle individual adipocytes with their nuclei protruding into the fat space (Fig. 13A). They are associated with prominent nuclear karyorrhexis, fat necrosis, and histiocytes, many with intracytoplasmic nuclear debris. Vascular invasion may be seen. Other inflammatory cells, particularly B-cells and plasma cells are absent or only present in small number.[54] The tumor cells are TCR-βF1 positive T-cells that express CD8, TIA-1, granzyme B, and perforin. There may be loss of CD2, CD5, and/or CD7. Staining for CD30, CD56, and EBV is negative. CD4 is also negative in the neoplastic lymphocytes but weak staining is often seen in the associated histiocytes. Staining for Ki67 reveals a high proliferation fraction and highlights the neoplastic lymphocytes rimming individual adipocytes (Fig. 13B).[54] T-cell receptor genes are clonally rearranged and recurrent mutations in genes associated with epigenetic regulation as well as PI3K/AKT/mTOR and JAK-STAT signal transduction pathways may be present.[112,113] In addition, biallelic germline mutations of the *HAVCR2* gene which encodes T cell immunoglobulin and mucin domain-containing protein 3 (TIM3), have recently been documented in a high percentage of patients with SCPTL, leading to protein misfolding and loss of its inhibitory receptor function.[110,114,115] This phenomenon is more frequently encountered in patients of Asian or Polynesian ancestry than those of European descent and is associated with a younger age at presentation, HLH and shorter relapse free survival.[110,114,115] First-line treatment for uncomplicated SPTCL is corticosteroids or other immunomodulatory therapy with a 5-year survival of 90%. Mulitiagent chemotherapy is reserved for cases that fail to respond or in cases with HLH, the latter associated with a much poorer prognosis with survival rate dropping to below 50%.[108]

Some cases of primary cutaneous γ/δ T-cell lymphoma can show considerable pathologic overlap with SPTCL, but these 2 entities should be relatively easy to distinguish using antibodies specific for α/β T-cells (TCR-βF1) and γ/δ T-cells (eg, anti-TCR-δ clone H-41). Separating SPTCL form lupus erythematosus profundus (LEP) can be more problematic. Histologically, numerous plasma cells, hyalinization of subcutaneous fat, reactive germinal centers, interface changes in the overlying epidermis, and clusters of plasmacytoid dendritic cells are typical of LEP but not SPTCL.[108,116] Conversely, rimming of adipocytes by

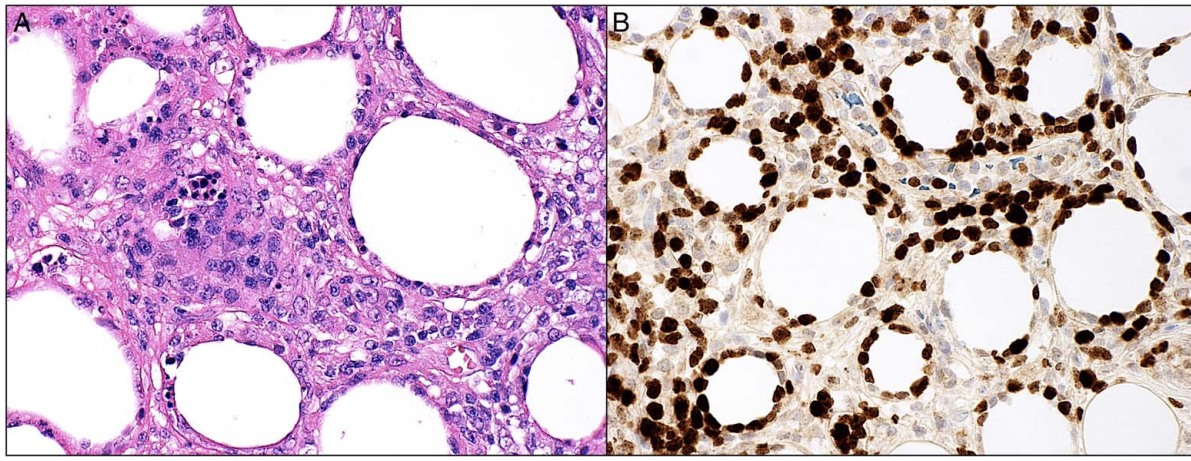

FIGURE 13. Subcutaneous panniculitis-like T-cell lymphoma (SPTCL). A, Neoplastic cells are seen encircling individual adipocytes and forming small aggregates between fat cells. There is associated karyorrhectic nuclear debris. B, Staining for Ki67 highlights the periadipocytic lymphoid cells. This staining pattern can help differentiate SPTCL from lupus erythematosus profundus. Please see this image in color online.

atypical T-cells displaying a high proliferation fraction and demonstration of clonal T-cell receptor gene rearrangements favor SCPTL.[116,117] However, it is increasingly recognized that a group of patients exists in which biopsies show features of both SPTCL and LEP. This is perhaps unsurprising given the known association between SPTCL patients and autoimmune disease, and highlights the need to look carefully for foci suggestive of SPTCL even when the dominant picture is that of LEP, and also to test perform serology for autoimmune disease even when the picture is more typical of SPTCL.[118]

Primary Cutaneous Gamma-Delta T-Cell Lymphoma

Primary cutaneous gamma-delta T-cell lymphoma (PCGDTCL) is a rare tumor of adults. Pateints present with widspread patches, plaques, nodules, and tumors with ulceration common.[108,119,120] There is frequent dissemination to mucosal and other extranodal sites but lymph node, spleen and bone marrow involvement is uncommon.[108,119,120] B-symptoms are often present and ~25% of patients develop haemophagocytic lymphohistiocytosis.[108,119,120]

The pattern of cutaneous infiltration is varied, including predominantly epidermotropic and/or dermal and subcutaneous variants, and often correlates with the clinical appearance: epidermotropism associated with patches and plaques while dermal and subcutaneous infiltrates more often correlate with tumors (Fig. 14A, B). Individual tumor cells are typically of medium to large size with coarsely clumped chromatin.[121] Angioinvasion and necrosis may be encountered. Epidermotropic infiltrates can resemble other forms of epidermotropic T-cell lymphoma while subcutaneous variants show significant morphologic overlap with SPTCL with rimming of adipocytes, prominent apoptosis, and abundant karyorrhectic debris (Fig. 14B). However, in contrast to subcutaneous panniculitis-like T-cell lymphoma, there is often involvement of septae as well as the overlying dermis.[122] Immunophenotyping and clinical correlation is therefore essential for diagnosis.

By definition, the tumor cells have a γ/δ phenotype, confirmed by positive staining for TCR-γ or TCR-δ (Fig. 14C). Expression of the Vδ1 isoform of the T-cell receptor is associated with epidermotropic and/or dermal centered PCGDTCL while PCGDTCL with predominantly subcutaneous distribution express Vδ2.[123] Staining for TCR-βF1 is negative. CD5 is characteristically absent but other T-cell-associated antigens such as CD2, CD3, and CD7 are generally retained. There is strong expression of cytotoxic molecules but most cases are negative for CD4 and CD8. CD56 is frequently but not always positive, particularly in subcutaneous infiltrates. The staining for EBV is negative.[108,119–121] TCR-γ or TCR-δ genes are clonally rearranged. The TCR-β gene may also be clonally rearranged but is never expressed.[120] Mutations in the JAK/STAT, MAPK, MYC, and chromatin modification pathways are common.[123]

Distinguishing PCGDTL from SPTCL is relatively straightforward if the pathologist has access to the appropriate antibodies for determining an α/β TCR or γ/δ phenotype. Additional clues that should raise suspicion of PCGDTL and prompt appropriate additional staining include involvement of the dermis and/or epidermis by neoplastic lymphocytes, negative staining for both CD4 and CD8, loss of CD5 and expression of CD56. When epidermotropism is present, the differential diagnosis includes MF, PR, LyP type D, and pcAECTL (Table 3). Demonstration of a γ/δ phenotype largely precludes a diagnosis of PR, LyP type D, and pcAECTL but distinction from MF can be more problematic in certain instances. Both the ICC and WHO classifications recognize MF with a γ/δ phenotype provided the clinical picture is typical, that is, slowly evolving patches and plaques. An indolent variant of PCGDTL is not currently recognized. However, studies have shown that epidermotropic PCGDTL expressing the Vδ1 isoform have a better prognosis than deeper lying Vδ2 positive cases despite sharing a similar mutational profile, and may display a clinical phenotype typical for MF, including response to skin directed therapies.[120,123,124] Despite displaying a prolonged phase of indolent growth, a proportion of these cases subsequently assume a clinical phenotype indistinguishable from the typical aggressive form of PCGDTL with rapid progression leading to death after a median of 16.5 months.[123] Thus, while it may be appropriate to manage such cases as MF in the first instance it may be prudent to closely follow them throughout the duration of their disease.

PCGDTL is treated with systemic polychemotherapy, but the response is poor, and the prognosis is dismal with a median survival of 31 months. Allogeneic stem cell transplant may offer a better chance of longer-term remission.[120] PCGDTL with epidermotropic features may have a better outcome compared with cases centered in subcutaneous fat; the presence of HLH and extracutaneous spread are associated with an even more unfavorable outcome.[108,119,120,123]

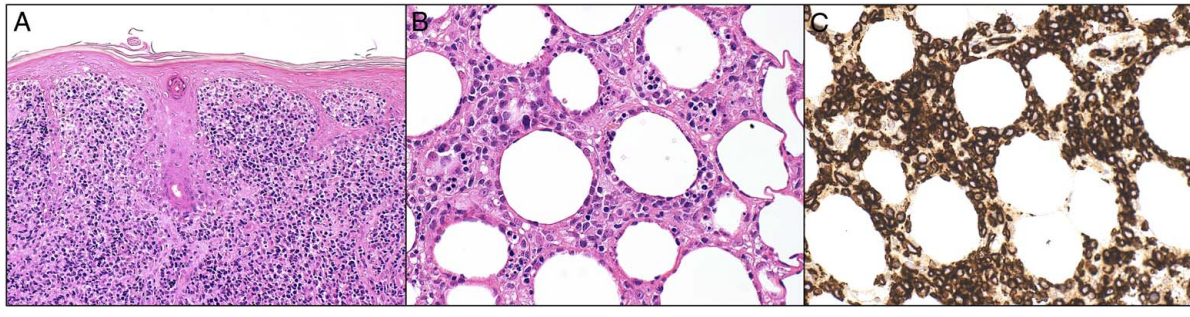

FIGURE 14. The pattern of infiltration in primary cutaneous γ/δ T-cell lymphoma is varied. A, This example shows a predominantly dermal distribution with some epidermotropism also present. B, Some cases preferentially involve subcutaneous fat and show significant histologic overlap with subcutaneous panniculitis-like T-cell lymphoma. C, Positive staining for TCR- δ confirms a γ/δ phenotype which is required for diagnosis. Please see this image in color online.

CONCLUDING REMARKS

Classification and diagnosis of primary cutaneous lymphoma require a multidisciplinary approach. Despite recent advances in our knowledge of the mutational landscape of many of these tumors and the availability of an ever-increasing array of monoclonal antibodies for phenotyping cutaneous infiltrates, clinical correlation remains essential for reliable separation of many entities, particularly those with a propensity to infiltrate the epidermis. However, although molecular analysis has a limited role to play in current diagnostic practice, it may increasingly point the way to future classifications and is already proving useful in identifying novel treatments for primary cutaneous lymphomas with a historically poor response to conventional chemotherapy.

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