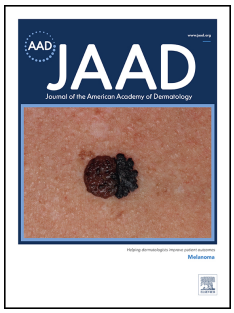

Primary cutaneous T-cell lymphomas other than Mycosis Fungoides and Sezary Syndrome – Part I: Clinical and histologic features and diagnosis.

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Abstract

Primary cutaneous T-cell lymphomas (CTCLs) are defined as lymphomas with a T-cell phenotype that present in the skin without evidence of systemic or extracutaneous disease at initial presentation. CTCLs other than Mycosis Fungoides (MF) and Sézary syndrome (SS) account for approximately one-third of CTCLs and encompass a heterogenous group of non-Hodgkin lymphomas ranging from indolent lymphoproliferative disorders to aggressive malignancies with a poor prognosis. The spectrum of CTCLs continues to broaden as new provisional entities are classified. Given the morphologic and histologic overlap among CTCLs and other diagnoses, a thorough clinical history, physical evaluation, and clinicopathologic correlation are essential in the workup and diagnosis of these rare entities. This article will summarize the epidemiologic, clinical, pathologic, and diagnostic features of CTCLs other than MF and SS.

I. Introduction

Primary cutaneous T-cell lymphomas (CTCLs) are non-Hodgkin lymphomas with Mycosis Fungoides (MF) and Sezary Syndrome (SS) most commonly recognized.[1, 2] However, there are several other variants listed in the World Health Organization (WHO)-European Organization for Research and Treatment of Cancer (EORTC) classification.[1, 3] After MF (60% of CTCL), primary cutaneous CD30+ lymphoproliferative disorders including lymphomatoid papulosis and primary cutaneous anaplastic large cell lymphoma comprise 30% of CTCLs.[4] Other CTCL subtypes [<10%] include subcutaneous panniculitis-like T-cell lymphoma, primary cutaneous gamma-delta T-cell lymphoma, primary cutaneous CD4+ small/medium T-cell lymphoproliferative disorder, primary cutaneous acral CD8+ T-cell lymphoma, and primary cutaneous CD8+ aggressive epidermotropic cytotoxic T cell lymphoma.[3]

These subtypes are heterogeneous in clinical presentation and course, and while rare, may first present to a dermatologist. In part 1 of this review, we summarize the clinical, histologic and immunophenotypic features of these non-MF/SS CTCLs. We also briefly discuss other systemic T-cell lymphomas with cutaneous manifestations.

II. CD30+ lymphoproliferative disorders

Primary cutaneous CD30-positive T-cell lymphoproliferative disorders (CD30+ LPD) are generally indolent and include lymphomatoid papulosis (LyP), primary cutaneous anaplastic large cell lymphoma (pcALCL), and “borderline” overlap lesions. The atypical T-cells express transmembrane receptor CD30 or Ki-1 antigen that is involved in T-lymphocyte immune response through downstream signaling pathways.[5] LyP and pcALCL can look histologically identical and are distinguished by clinical appearance and disease course (Table I).[6]

Lymphomatoid Papulosis

Clinical Features

LyP is the second most common CTCL (12% of all primary cutaneous lymphomas), characterized by waxing and waning crops of erythematous papules or nodules that spontaneously regress over several weeks (Figure 1).[1, 7, 8] Some experts consider this a benign lymphoproliferative condition, while others consider it a low-grade CTCL. LyP lesions can be symptomatic (pruritic/painful), grouped/agminate or generalized, and variable in number and episode frequency.[9-18] Less common morphologic variants include plaque-like, follicular, bullous, and pustular LyP.[19-23] Scaling/crusting, ulceration (particularly type E), varioliform scarring or hyperpigmentation may occur.[24, 25]

The incidence of LyP is 1.2 to 1.9 cases per 1,000,000 people.[27] The median age of onset is ~50 (although seen in younger patients), with slight male predominance.[26-29] The 5-year survival is excellent (approaching 100%); however, secondary cutaneous lymphomas may occur in 15.5-50% of cases (MF most commonly, or pcALCL), with rare systemic lymphomas (Hodgkin lymphoma) (4-12%).[1, 28-34] Although no definitive risk factors have been identified, some studies have suggested that LyP subtypes B and C, facial involvement, frequent LyP recurrences, older age, fascin expression by CD30+ cells, and detectable T-cell clone are associated with the development of a second malignancy.[29, 35-38]

Histologic and Immunophenotypic Features

There are five recognized histologic LyP subtypes (A-E) and one genetic phenotype, chromosome 6p25.3 rearrangement (Table II), although additional patterns have been reported.[3,

[39-42] More than one subtype may be present in a single patient, and the subtypes do not appear to have prognostic or therapeutic implications.[43,44]

The most common pattern is type A (75-80% of patients), characterized by large CD30+ lymphocytes in a robust background of histiocytes, neutrophils, and eosinophils in the dermis. Lymphocytes exhibit a T-helper phenotype (CD3+, CD4+, CD45RO+), with loss of pan T-cell markers (CD2, CD3, CD5, and CD7).[45] The epidermotropism of atypical T-cells in type B may mimic MF. In type C, sheets of CD30+ cells invoke the histologic differential of pcALCL or MF with large cell transformation (latter typically presents with tumors clinically). Type D, floridly CD8-positive, can histologically mimic other CD8+ CTCL subtypes.[46-48] Angiocentric Type E (clinical presentation of crateriform ulcers) must be distinguished from reactive processes as well as CD30+ systemic lymphomas. Chromosomal rearrangements of the *DUSP22-IRF4* locus on 6p25.3 may have a biphenotypic cytology in LyP (small intraepidermal lymphocytes, and large pleomorphic cells in the dermis).[39] Monoclonal T-cell receptor (TCR) gene rearrangements, including TCRγ/δ, may be detected in LyP, although this has also been seen in reactive CD30+ conditions including pityriasis lichenoides.[49-55]

Primary cutaneous anaplastic large cell lymphoma

Clinical Features

PcALCL presents as rapidly-growing, solitary or localized group of nodule(s) that may ulcerate (Figure 2). It typically occurs in the 6th decade of life, has a slight male predominance, and may be associated with immunosuppression (e.g. HIV or post-organ transplantation). The nodules are larger than LyP, rarely multifocal (20%), with predilection for the head, neck, and extremities.[56-58] PcALCL less commonly partially or completely regress (10%-42%), and relapse is common.[28, 34] Extracutaneous dissemination can occur (10-15% of patients), usually

with regional lymph node involvement.[3, 24] Staging with computed tomography (CT) or positron emission tomography/computed tomography (PET/CT) is recommended to exclude systemic ALCL (sALCL) with cutaneous involvement.[4]

Breast implant-associated ALCL has been recently recognized in women with textured breast implants, after median of 6-13 years.[59-63] Patients present with delayed spontaneous seroma, asymmetric breast swelling, or pain.[64] Most cases are successfully treated by implant removal and full capsulectomy,[62] although current NCCN guidelines recommend staging with PET/CT.[65]

Histologic and Immunophenotypic Features

PcALCL consists of nodular or multinodular infiltrate of large lymphocytes in the dermis and sometimes upper subcutis (Figure 3A). The lymphocytes contain eosinophilic or amphophilic cytoplasm with irregular horseshoe or kidney-shaped nuclei.[66-68] By definition, 75% of cells must express CD30 (Figure 3B).[1, 69] These typically express CD4, but CD8 and cytotoxic markers (granzyme B, TIA-1, perforin) are expressed in over 50% of cases.[67-71] Cutaneous lymphocyte antigen (CLA) is positive, and epithelial membrane antigen (EMA) is negative in pcALCL, unlike in sALCL.[68] Anaplastic lymphoma kinase (*ALK*) translocation, t(2;5), common in sALCL, is rare in pcALCL, although ALK-positive cutaneous-only disease has been described, and ALK-negativity is seen in 40-50% of systemic involvement.[66, 72] Monoclonal TCR gene rearrangements are found in ≥ 90% of pcALCL. Chromosomal rearrangement of the *DUSP22-IRF4* locus on 6p25.3 has been detected in 28% of cases (also seen in sALCL and LyP).[68]

III. Subcutaneous panniculitis-like T-cell lymphoma

Clinical Features

Subcutaneous panniculitis-like T-cell lymphoma (SPTCL) clinically mimics panniculitis (Figure 4)[73, 74] with female predominance and younger age of presentation (median age 36 but some studies reporting 20% of patients under 20 years).[75] In 2005, the WHO-EORTC restricted SPTCL to those expressing αβ T-cell receptors, distinguishing from the more aggressive γδ T-cell lymphoma which can also present with panniculitic lesions.[1] SPTCL presents as subcutaneous, indurated plaques and nodules involving lower extremities and less commonly upper extremities and trunk.[75, 76] Lesions rarely ulcerate and resolve with lipoatrophy and calcification.[75, 77] PET/CT is used to assess baseline cutaneous disease extent and treatment response.[78, 79]

Systemic constitutional "B" symptoms [fevers, night sweats, and weight loss] may be present in up to 60% of cases, and patients may have cytopenias and transaminitis.[75] Associated autoantibodies and autoimmune diseases, primarily systemic lupus erythematosus, but also sarcoidosis, dermatomyositis, Sjogrens syndrome, and rheumatoid arthritis occur in 13%-40% of patients.[74, 75, 80] Hemophagocytic syndrome (HPS), a syndrome of excessive immune activation characterized by fever, splenomegaly, and hemophagocytosis in bone marrow, spleen, lymph node, or liver with lab abnormalities (cytopenias, hypertriglyceridemia, and hyperferritinemia), has been observed in 7-45% in various studies and may be associated with worse outcome.[74-77, 80, 81]

Histologic and Immunophenotypic Features

SPTCL can mimic other inflammatory panniculitides, including lupus erythematosus panniculitis (LEP), and presents as a lobular panniculitis of atypical small or medium lymphocytes with irregular hyperchromatic nuclei.[1] Neoplastic lymphocytes form a rim around adipocytes, and fat necrosis, karyorrhexis, and cytophagocytosis are common (Figure 5A).[75, 82, 83] The cells express CD8+ phenotype (granzyme, TIA-1, and perforin), are positive for βF1, and negative for CD30, TCRγ/δ, CD56, and EBV, distinguishing from gamma/delta T-cell lymphoma (PCGD-TCL) and extranodal NK/T-cell lymphoma (ENKTCL) (Figure 5B).[75, 84, 85] Germline and somatic mutations in *HAVCR2*, encoding immune response modulator, T-cell immunoglobulin mucin 3 (TIM-3), can be seen and may be associated with HPS.[86] Monoclonal TCR gene rearrangement is seen in most cases.

SPTCL's cytotoxic immunophenotype, uncommon in LEP (which is comprised of T-helper and B cells), is a helpful distinguishing feature.[87-89] Rimming and erythrophagocytosis are more common in SPTCL, but have been described in both entities. In early SPTCL, histiocytes, neutrophils, and plasma cells are commonly observed in the absence of significant atypia, adding to diagnostic difficulty.[84,90] Aggregates of CD123+ plasmacytoid dendritic cells and lymphoid follicles with germinal centers and mucin deposition are more characteristic of LEP.[91] It has been suggested that Ki-67 and retention of CD7 can be useful in discriminating SPTCL from LEP.[92]

IV. Primary cutaneous CD4+ small/medium T-cell lymphoproliferative disorder and Primary cutaneous acral CD8+ T-cell lymphoma

Primary cutaneous CD4+ small/medium T-cell lymphoproliferative disorder

Clinical Features

Primary cutaneous CD4+ small/medium T-cell lymphoproliferative disorder (PCSM-TCLPD) is an indolent T-cell lymphoproliferative disorder presenting as a solitary erythematous papule,

nodule, or plaque, with predilection for the head and neck, followed by upper trunk (Figure 6).[1, 93-95] Multifocal lesions are rare.[96, 97] It is typically seen in adults over 50 years, although pediatric cases have been reported.[97-101]

Histologic and Immunophenotypic Features

A nodular or diffuse infiltrate of small-to-medium sized pleomorphic lymphocytes in the dermis, and frequently the subcutis, is observed (Figure 7A).[97, 102] Focal epitheliotropism and reactive infiltrates of B-cells, plasma cells, and/or histiocytes are common.[93, 94, 99, 103] Neoplastic cells are CD3+, CD4+, CD8-, CD30-, and negative for cytotoxic markers (Figure 7B). Expression of PD-1, BCL6, and CXCL13 suggests a T-follicular helper phenotype, although the Ki67 proliferation index is low (5-30%), distinguishing from systemic lymphoma.[99, 102-105] Monoclonal TCR gene rearrangements are detected in 60-100% of cases.[106, 107]

Primary cutaneous acral CD8+ T-cell lymphoma

Clinical Features

Primary cutaneous acral CD8+ T cell lymphoma (Acral CD8+ TCL) is also indolent, presenting in adults older than 50 years as a solitary papule or nodule on the ear or other acral sites (e.g. nose, hands, and feet) (Figure 8).[108-111] Multifocal presentation is rare. While PCSM-TCLPD may share clinicopathologic features with acral CD8+ TCL, the CD4+ vs CD8+ phenotypes are distinctive (Table III).[112-114]

Histologic and Immunophenotypic Features

Diffuse dermal and sometimes subcutaneous cutaneous infiltrates of bland, medium-sized neoplastic cells with irregular nuclei and little cytoplasm are seen.[3, 108, 110] Necrosis, ulceration, and angiocentricity are absent, and mitoses are rare.[108, 115] Tumor cells are CD3+, CD4-, CD8+, CD30-, and often CD68+ (dot-like pattern).[116] Cytotoxic markers may be negative. EBV is

negative and Ki-67 proliferation index is low, distinguishing from aggressive subtypes.[3, 108-110] Monoclonal TCR gene rearrangements are usually present.

VII. Aggressive non-MF/SS CTCL

Primary cutaneous CD8+ aggressive epidermotropic cytotoxic T cell lymphoma

Clinical Features

Primary cutaneous CD8+ aggressive epidermotropic cytotoxic T cell lymphoma (AECTCL) presents as rapidly progressing nodules/tumors or annular hyperkeratotic patches and plaques with early ulceration/necrosis [3, 117-120]. (Figure 9). The disease primarily affects older males (median age 77).[117, 121, 122] A poorly defined eczematous or psoriasiform rash may precede abrupt AECTCL eruption.[117, 123] Oral mucosa and genital skin may be involved, and extracutaneous spread is seen (e.g. lungs, adrenal glands, central nervous system), although lymph node and bone marrow involvement is uncommon.[117, 119, 124]

Histologic and Immunophenotypic Features

Histologic features can mimic MF with epidermotropic lymphoid infiltrate showing scattered pagetosis and epidermal aggregates resembling Pautrier microabscesses. However, the lymphocytes are large and invade the epidermis in a dense front.[125] Hyperkeratosis or acanthosis is seen in early papulosquamous presentations, with infiltrates extending to the deep dermis or subcutis in tumor lesions. Invasion and/or destruction of the vasculature and adnexal structures is common.[1, 126, 127] Atypical lymphocytes are CD8+, and express cytotoxic markers granzyme B+, perforin+ and TIA-1+.[90, 118, 119, 128]. Most cases retain CD7.[129] The Ki-67 proliferation index is high, and EBV and CD56 are negative.[119, 126] In general, AETCL is regarded as TCR αβ+.[119]

The histologic differential diagnosis includes other CD8+ CTCLs including LyP type D, pcALCL, or CD8+ MF. The latter presents as hyper- or hypopigmented patches or as solitary psoriasiform or hyperkeratotic patch/plaque(s) on the lower extremities in pagetoid reticulosis, both with indolent course.

Primary cutaneous gamma-delta T-cell lymphoma

Clinical Features

Primary cutaneous gamma-delta T-cell lymphoma (PCGDTCL) is aggressive, presenting as multiple deep plaques or nodules/tumors on the lower extremities [less commonly trunk and upper extremities] of patients in the 6th decade of life (Figure 10).[130-132] Lesions may mimic panniculitis, but often become progressively ulceronecrotic, unlike inflammatory panniculitides or SPTCL. Other clinical presentations include scaly plaques resembling mycosis fungoides or psoriasis which later ulcerate. The extent of skin disease (solitary/localized versus generalized) does not appear to correlate with prognosis.[133]

B-symptoms are common in PCGDTCL as is HPS with fever, cytopenias, and hepatosplenomegaly.[134, 135] While HPS can involve hepatosplenomegaly, true gastrointestinal involvement is rare, and lymph node and bone marrow involvement is uncommon.

Histologic and Immunophenotypic Features

The heterogeneity of histological patterns, hitherto lack of reliable standard immunohistochemical markers for detection of TCR γ/δ chains, and the presence of reactive γδ T-cell subsets in indolent CTCLs have made PCGDTCL a challenging diagnosis.[55, 129, 136] The diagnosis should be made directly by detection of TCR γ or δ staining on tissue specimens, as the

absence of βF1 expression is non-specific and can be seen in other lymphomas including MF (Figure 11).

PCGDTCL infiltrates the subcutaneous tissue and, unlike SPTCL, frequently involves the epidermis and upper dermis, with multiple histologic patterns possible in the same patient.[131, 133]There may be some similarities to SPTCL such as rimming, or to MF with cerebriform lymphocytes, epidermotropism, or pagetoid reticulosis-like infiltrates.[133, 137] Apoptosis, necrosis, and angioinvasion with angiodestruction are frequently observed, and macrophages engulfing lymphocytes or other cell types can be seen.[75] The lymphocytes are medium or large in size, and often exhibit a double negative (CD4- CD8-) phenotype; however, some cases express CD8, and variable positivity for other cytotoxic markers and CD56.[1, 133, 138, 139] EBV is negative. Monoclonal TCR gene rearrangements are typically seen.[132, 140]

The PCGDTCL immunophenotype can overlap with other aggressive entities- EKNTCL, nasal type and AECTCL (Table IV). Although γδ T-cell expression can be seen in other cutaneous lymphomas and reactive conditions, a recent study showed that γδ T-cells comprise a minority of lymphocytes in these entities (< 25% of lymphocyte population).[55]

PCGDTCL has until recently been understood as an aggressive lymphoma. Recent research suggests that clinical-pathological and molecular features may have some bearing on prognosis, with patch-like epidermotropic lesions (often demonstrating a bias toward TCR-delta Vbeta1) possibly showing a better outcome while deeper lesions tend to have poor prognoses as traditionally thought.[141, 142]

VI. Other T-cell lymphomas presenting in the skin

These rare usually systemic T-cell lymphomas share an aggressive course and have non-specific cutaneous manifestations. Salient features of the more common systemic T-cell

lymphomas involving the skin are included here (Extranodal NK/T cell lymphoma, nasal-type, Chronic active EBV infection, Adult T-cell leukemia/lymphoma; Angioimmunoblastic T-cell lymphoma, and Peripheral T-cell lymphoma- not otherwise specified). Other peripheral T-cell lymphomas and leukemias (including T-cell prolymphocytic leukemia) can also present with cutaneous involvement, but detailed characteristics of these entities are beyond the scope of this review.[143]

Extranodal NK/T cell lymphoma (ENKTCL), nasal-type is an aggressive EBV-associated, cytotoxic NHL, common in Asia and Central and South America (up to 10% of NHL) and rare in the U.S. (less than 2% of NHL).[144-151] The nasopharynx and upper aerodigestive tract are most commonly involved, with skin the most common site of secondary involvement. Skin is the primary disease site in 10% of cases with erythematous to violaceous, ulcerative plaques or tumors involving the trunk and extremities.[129] Histology shows perivascular atypical lymphoid infiltrate, expressing CD4, CD56, and EBER-ISH. Cases may or may not demonstrate monoclonal TCR gene rearrangements.

Chronic active EBV infection (CAEBV) is characterized by persistent infectious mononucleosis-like syndrome and EBV viremia in an apparent immunocompetent host.[152] CAEBV was initially thought to be a childhood disease, however, increasing adult cases have been identified.[153, 154] Skin manifestations include hydroa vacciniforme-like LPD (HV-like LPD) and hypersensitivity reactions to mosquito bites. HV-like LPD presents with papulovesicular eruption on sun-exposed areas, while mosquito bite hypersensitivity presents as ulceronecrotic lesions at mosquito bite sites. Prognoses vary, with some patients remaining stable with skin-limited disease and others developing multiorgan dysfunction and progression to lymphoma.[3, 152]

Adult T-cell leukemia/lymphoma (ATLL) is a peripheral T-lymphocytic malignancy associated with human T-lymphotropic virus, type I (HTLV-I) infection, and is seen in patients from Japan, Caribbean, South America, and West Africa where HTLV is endemic.[120] Cutaneous manifestations occur in 39% to 72% of cases, more frequently in chronic and smoldering subtypes, and may be the initial presentation in one-third of patients.[155] Rarely, ATLL may only present in the skin, often as nodulotumoral lesions, though it may be heterogenous (multipapular eruption, plaques, patches, and erythroderma) (Figure 12). Increased overall survival in skin-first ATLL has been reported compared to skin-second/skin-uninvolved patients.[155] ATLL often histologically mimics advanced CTCL, with large-cell morphology and a CD4+ TCR αβ phenotype similar to MF. CD25 is strongly positive, and CD30 may be expressed. HTLV serologic confirmation is typically used for diagnosis while viral integration studies are the gold standard.[156]

Angioimmunoblastic T-cell lymphoma (AITL) accounts for 15-20% of peripheral T cell lymphomas (PTCL), arising from CD4+ T-follicular-helper cells[157-161] The skin is affected in ~50% of cases and presents with macules, papules, or plaque-like/nodular eruptions.[162] AITL is frequently EBV-positive.[163, 164] Histology can be subtle in the skin, and immunophenotypic similarities to PCSM-TCLPD may only be resolved by clinical correlation.

PTCL-NOS is a heterogenous group of lymphomas that do not meet criteria for other types of T-cell lymphomas. In our experience, PTCL-NOS typically presents as erythematous-violaceous nodules or plaques (Figure 13). Histology and immunophenotype may vary. Further research is needed to better characterize this group.

VII. Conclusion

Non-MF/non-SS CTCLs are heterogeneous, ranging from generally indolent lymphoproliferative disorders to aggressive malignancies with poor prognoses. Given the rarity and variable presentations, key clinical, histologic, and immunophenotypic features are essential in making the diagnosis. Current research efforts are focused on better classifying these subtypes and evaluating prognostic and therapeutic markers.

Abbreviation and acronym list:

AECTCL, primary cutaneous CD8+ aggressive epidermotropic cytotoxic T cell lymphoma; AITL, angioimmunoblastic T-cell lymphoma; Acral CD8+ TCL, acral CD8+ T-cell lymphoma; ATLL, adult T-cell leukemia/lymphoma; CD30+ LPD, Primary cutaneous CD30+ lymphoproliferative disorders; CAEBV, Chronic active EBV infection; CTCL, cutaneous T-cell lymphoma; EBV, Epstein-Barr Virus; ENKTL, extranodal NK/T cell lymphoma; EORTC, European Organization of Research and Treatment of Cancer; HPS, hemophagocytic syndrome; HTLV-1, human T-cell lymphotropic virus type-1; HV-like LPD, hydroa vacciniforme-like LPD; ISCL, International Society for Cutaneous Lymphomas; LyP, lymphomatoid papulosis; MF, mycosis fungoides; pcALCL, primary cutaneous anaplastic large cell lymphoma; PCGDTCL, primary cutaneous gamma-delta T-cell lymphoma; PCSM-TCLPD, primary cutaneous CD4+ small-medium sized lymphoproliferative disorder; PTCL-NOS, Peripheral T-cell lymphoma, not otherwise specified; SPTCL, subcutaneous panniculitis-like T-cell lymphoma; SS, Sézary syndrome; TCR, T-cell receptor; T-PLL, T-cell prolymphocytic leukemia

References

1. Willemze R, Jaffe ES, Burg G, Cerroni L, Berti E, Swerdlow SH et al. WHO-EORTC classification for cutaneous lymphomas. Blood 2005;105:3768-85.
2. Jawed SI, Myskowski PL, Horwitz S, Moskowitz A , Querfeld C. Primary cutaneous T-cell lymphoma (mycosis fungoides and Sezary syndrome): part I. Diagnosis: clinical and histopathologic features and new molecular and biologic markers. J Am Acad Dermatol 2014;70:205.e1-16; quiz 21-2.
3. Willemze R, Cerroni L, Kempf W, Berti E, Facchetti F, Swerdlow SH et al. The 2018 update of the WHO-EORTC classification for primary cutaneous lymphomas. Blood 2019;133:1703-14.
4. Kempf W, Kerl K , Mitteldorf C. Cutaneous CD30-positive T-cell lymphoproliferative disorders-clinical and histopathologic features, differential diagnosis, and treatment. Seminars in cutaneous medicine and surgery 2018;37:24-9.
5. Pierce JMR , Mehta A. Diagnostic, prognostic and therapeutic role of CD30 in lymphoma. Expert Review of Hematology 2017;10:29-37.
6. Oschlies I, King RL, Dotlic S, Montes-Moreno S, Ponzoni M, Traverse-Glehen A et al. The clinico-pathological spectrum of primary cutaneous lymphoma other than mycosis fungoides/Sezary syndrome. Virchows Archiv : an international journal of pathology 2019.
7. Martinez-Cabriales SA, Walsh S, Sade S , Shear NH. Lymphomatoid papulosis: an update and review. 2020;34:59-73.
8. Macaulay WL. Lymphomatoid papulosis. A continuing self-healing eruption, clinically benign--histologically malignant. Archives of dermatology 1968;97:23-30.
9. Scarisbrick JJ, Evans AV, Woolford AJ, Black MM , Russell-Jones R. Regional lymphomatoid papulosis: a report of four cases. British Journal of Dermatology 1999;141:1125-8.
10. González-López MA, González-Vela MdC, Caballero C, Consuegra G, Fernández-Llaca H , Piris MA. Localized lymphomatoid papulosis. International Journal of Dermatology 2015;54:e98-e100.
11. Wang T, Guo CL, Xu C-C, Zhou X-P, Liu Y-H , Zheng H-Y. Regional lymphomatoid papulosis in association with pseudoepitheliomatous hyperplasia: 13 years follow-up. 2015;29:1853-4.
12. Hsu Y-J, Su L-H, Hsu Y-L, Tsai T-H , Hsiao C-H. Localized lymphomatoid papulosis. Journal of the American Academy of Dermatology 2010;62:353-6.
13. Yancovitz M, Walters RF, Kamino H , Brown LH. Acral lymphomatoid papulosis. Journal of the American Academy of Dermatology 2010;62:530-1.
14. Dalle S, Balme B , Thomas L. Lymphomatoid papulosis localized to the face. Dermatology online journal 2006;12:9.
15. Kluk J, Child F , Robson A. Lymphomatoid papulosis with 6p25.3 rearrangement: a further case of the newly described variant. British Journal of Dermatology 2014;171:1590-2.
16. Steinhoff M, Assaf C , Sterry W. Persistent agmination of lymphomatoid papulosis: Not a new entity, but localized lymphomatoid papulosis. Journal of the American Academy of Dermatology 2008;59:164-5.
17. Heald P, Subtil A, Breneman D , Wilson LD. Persistent agmination of lymphomatoid papulosis: An equivalent of limited plaque mycosis fungoides type of cutaneous T-cell lymphoma. Journal of the American Academy of Dermatology 2007;57:1005-11.

18. Fujimura T, Lyu C, Tsuchiyama K , Aiba S. CD30-Positive Angioinvasive Lymphomatoid Papulosis (Type E) Developing from Parapsoriasis en Plaque. Case Reports in Oncology 2018;11:850-4.
19. Kempf W, Kazakov DV, Baumgartner H-P , Kutzner H. Follicular lymphomatoid papulosis revisited: A study of 11 cases, with new histopathological findings. Journal of the American Academy of Dermatology 2013;68:809-16.
20. Barnadas MA, López D, Pujol RM, García-Patos V, Curell R , de Moragas JM. Pustular lymphomatoid papulosis in childhood. Journal of the American Academy of Dermatology 1992;27:627-8.
21. Chimenti S, Fargnoli MC, Pacifico A , Peris K. Mucosal involvement in a patient with lymphomatoid papulosis. Journal of the American Academy of Dermatology 2001;44:339-41.
22. Sureda N, Thomas L, Bathelier E, Balme B, Depaepe L , Dalle S. Bullous lymphomatoid papulosis. Clinical and Experimental Dermatology 2011;36:800-1.
23. Pujol RM, Muret MP, Bergua P, Bordes R , Alomar A. Oral Involvement in Lymphomatoid Papulosis. Dermatology 2005;210:53-7.
24. Liu HL, Hoppe RT, Kohler S, Harvell JD, Reddy S , Kim YH. Cd30+ cutaneous lymphoproliferative disorders: The stanford experience in lymphomatoid papulosis and primary cutaneous anaplastic large cell lymphoma. Journal of the American Academy of Dermatology 2003;49:1049-58.
25. Kempf W. Cutaneous CD30-Positive Lymphoproliferative Disorders. Surgical Pathology Clinics 2014;7:203-28.
26. Wieser I, Wohlmuth C, Nunez CA , Duvic M. Lymphomatoid Papulosis in Children and Adolescents: A Systematic Review. American journal of clinical dermatology 2016;17:319-27.
27. Miquel J, Fraitag S, Hamel-Teillac D, Molina T, Brousse N, de Prost Y et al. Lymphomatoid papulosis in children: a series of 25 cases. The British journal of dermatology 2014;171:1138-46.
28. Bekkenk MW, Geelen FoAMJ, Vader PCvV, Heule F, Geerts M-L, van Vloten WA et al. Primary and secondary cutaneous CD30+lymphoproliferative disorders: a report from the Dutch Cutaneous Lymphoma Group on the long-term follow-up data of 219 patients and guidelines for diagnosis and treatment. Blood 2000;95:3653-61.
29. Wieser I, Oh CW, Talpur R , Duvic M. Lymphomatoid papulosis: Treatment response and associated lymphomas in a study of 180 patients. Journal of the American Academy of Dermatology 2016;74:59-67.
30. Kunishige JH, McDonald H, Alvarez G, Johnson M, Prieto V , Duvic M. Lymphomatoid papulosis and associated lymphomas: a retrospective case series of 84 patients. Clin Exp Dermatol 2009;34:576-81.
31. Cordel N, Tressières B, D'Incan M, Machet L, Grange F, Estève É et al. Frequency and Risk Factors for Associated Lymphomas in Patients With Lymphomatoid Papulosis. Oncologist 2016;21:76-83.
32. AbuHilal M, Walsh S , Shear N. Associated Hematolymphoid Malignancies in Patients With Lymphomatoid Papulosis: A Canadian Retrospective Study. Journal of cutaneous medicine and surgery 2017;21:507-12.
33. de Souza A, el-Azhary RA, Camilleri MJ, Wada DA, Appert DL , Gibson LE. In search of prognostic indicators for lymphomatoid papulosis: a retrospective study of 123 patients. J Am Acad Dermatol 2012;66:928-37.
34. Kempf W, Pfaltz K, Vermeer MH, Cozzio A, Ortiz-Romero PL, Bagot M et al. EORTC, ISCL, and USCLC consensus recommendations for the treatment of primary cutaneous CD30-

positive lymphoproliferative disorders: lymphomatoid papulosis and primary cutaneous anaplastic large-cell lymphoma. Blood 2011;118:4024-35.
35. Martinez-Cabriales SA, Walsh S, Sade S , Shear NH. Lymphomatoid papulosis: an update and review. Journal of the European Academy of Dermatology and Venereology 2020;34:59-73.
36. Nikolaou V, Papadavid E, Ekonomidi A, Dalamaga M, Marinos L, Stratigos A et al. Association of clinicopathological characteristics with secondary neoplastic lymphoproliferative disorders in patients with lymphomatoid papulosis. Leukemia & lymphoma 2015;56:1303-7.
37. Kempf W, Levi E, Kamarashev J, Kutzner H, Pfeifer W, Petrogiannis-Haliotis T et al. Fascin expression in CD30-positive cutaneous lymphoproliferative disorders. Journal of cutaneous pathology 2002;29:295-300.
38. Cordel N, Tressières B, D'Incan M, Machet L, Grange F, Estève É et al. Frequency and Risk Factors for Associated Lymphomas in Patients With Lymphomatoid Papulosis. Oncologist 2016;21:76-83.
39. Karai LJ, Kadin ME, Hsi ED, Sluzevich JC, Ketterling RP, Knudson RA et al. Chromosomal rearrangements of 6p25.3 define a new subtype of lymphomatoid papulosis. The American journal of surgical pathology 2013;37:1173-81.
40. El Shabrawi-Caelen L, Kerl H , Cerroni L. Lymphomatoid papulosis: reappraisal of clinicopathologic presentation and classification into subtypes A, B, and C. Arch Dermatol 2004;140:441-7.
41. Saggini A, Gulia A, Argenyi Z, Fink-Puches R, Lissia A, Magana M et al. A variant of lymphomatoid papulosis simulating primary cutaneous aggressive epidermotropic CD8+ cytotoxic T-cell lymphoma. Description of 9 cases. Am J Surg Pathol 2010;34:1168-75.
42. Kempf W, Kazakov DV, Scharer L, Rutten A, Mentzel T, Paredes BE et al. Angioinvasive lymphomatoid papulosis: a new variant simulating aggressive lymphomas. Am J Surg Pathol 2013;37:1-13.
43. Goodlad JR. The many faces of lymphomatoid papulosis. Diagnostic Histopathology 2014;20:263-70.
44. Martinez-Cabriales SA, Walsh S, Sade S , Shear NH. Lymphomatoid papulosis: an update and review. J Eur Acad Dermatol Venereol 2020;34:59-73.
45. Kempf W. A new era for cutaneous CD30-positive T-cell lymphoproliferative disorders. Semin Diagn Pathol 2017;34:22-35.
46. de Souza A, Camilleri MJ, Wada DA, Appert DL, Gibson LE , el-Azhary RA. Clinical, histopathologic, and immunophenotypic features of lymphomatoid papulosis with CD8 predominance in 14 pediatric patients. J Am Acad Dermatol 2009;61:993-1000.
47. Martires KJ, Ra S, Abdulla F , Cassarino DS. Characterization of primary cutaneous CD8+/CD30+ lymphoproliferative disorders. The American Journal of dermatopathology 2015;37:822-33.
48. Kempf W. Cutaneous CD30-Positive Lymphoproliferative Disorders. Surg Pathol Clin 2014;7:203-28.
49. Weiss LM, Wood GS, Trela M, Warnke RA , Sklar J. Clonal T-cell populations in lymphomatoid papulosis. Evidence of a lymphoproliferative origin for a clinically benign disease. The New England journal of medicine 1986;315:475-9.
50. Greisser J, Palmedo G, Sander C, Kutzner H, Kazakov DV, Roos M et al. Detection of clonal rearrangement of T-cell receptor genes in the diagnosis of primary cutaneous CD30 lymphoproliferative disorders. Journal of cutaneous pathology 2006;33:711-5.

51. Gellrich S, Wernicke M, Wilks A, Lukowsky A, Muche JM, Jasch KC et al. The cell infiltrate in lymphomatoid papulosis comprises a mixture of polyclonal large atypical cells (CD30-positive) and smaller monoclonal T cells (CD30-negative). The Journal of investigative dermatology 2004;122:859-61.
52. Steinhoff M, Hummel M, Anagnostopoulos I, Kaudewitz P, Seitz V, Assaf C et al. Single-cell analysis of CD30+ cells in lymphomatoid papulosis demonstrates a common clonal T-cell origin. Blood 2002;100:578-84.
53. Guitart J , Querfeld C. Cutaneous CD30 lymphoproliferative disorders and similar conditions: a clinical and pathologic prospective on a complex issue. Seminars in Diagnostic Pathology 2009;26:131-40.
54. Martinez-Escala ME, Sidiropoulos M, Deonizio J, Gerami P, Kadin ME , Guitart J. γδ T-cell-rich variants of pityriasis lichenoides and lymphomatoid papulosis: benign cutaneous disorders to be distinguished from aggressive cutaneous γδ T-cell lymphomas. The British journal of dermatology 2015;172:372-9.
55. Pulitzer M, Geller S, Kumar E, Frosina D, Moskowitz A, Horwitz S et al. T-cell receptor-delta expression and gammadelta+ T-cell infiltrates in primary cutaneous gammadelta T-cell lymphoma and other cutaneous T-cell lymphoproliferative disorders. Histopathology 2018;73:653-62.
56. Kadin ME , Carpenter C. Systemic and primary cutaneous anaplastic large cell lymphomas. Seminars in hematology 2003;40:244-56.
57. Bekkenk MW, Geelen FA, van Voorst Vader PC, Heule F, Geerts ML, van Vloten WA et al. Primary and secondary cutaneous CD30(+) lymphoproliferative disorders: a report from the Dutch Cutaneous Lymphoma Group on the long-term follow-up data of 219 patients and guidelines for diagnosis and treatment. Blood 2000;95:3653-61.
58. Paulli M, Berti E, Rosso R, Boveri E, Kindl S, Klersy C et al. CD30/Ki-1-positive lymphoproliferative disorders of the skin--clinicopathologic correlation and statistical analysis of 86 cases: a multicentric study from the European Organization for Research and Treatment of Cancer Cutaneous Lymphoma Project Group. 1995;13:1343-54.
59. Collett DJ, Rakhorst H, Lennox P, Magnusson M, Cooter R , Deva AK. Current Risk Estimate of Breast Implant–Associated Anaplastic Large Cell Lymphoma in Textured Breast Implants. Plastic and Reconstructive Surgery 2019;143.
60. Cordeiro PG, Ghione P, Ni A, Hu Q, Ganesan N, Galasso N et al. Risk of breast implant associated anaplastic large cell lymphoma (BIA-ALCL) in a cohort of 3546 women prospectively followed long term after reconstruction with textured breast implants. Journal of Plastic, Reconstructive & Aesthetic Surgery 2020;73:841-6.
61. Doren EL, Miranda RN, Selber JC, Garvey PB, Liu J, Medeiros LJ et al. U.S. Epidemiology of Breast Implant-Associated Anaplastic Large Cell Lymphoma. Plast Reconstr Surg 2017;139:1042-50.
62. Marra A, Viale G, Pileri SA, Pravettoni G, Viale G, De Lorenzi F et al. Breast implant-associated anaplastic large cell lymphoma: A comprehensive review. Cancer Treatment Reviews 2020;84:101963.
63. Mehta-Shah N, Clemens MW , Horwitz SM. How I treat breast implant–associated anaplastic large cell lymphoma. Blood 2018;132:1889-98.
64. Clemens MW, Medeiros LJ, Butler CE, Hunt KK, Fanale MA, Horwitz S et al. Complete Surgical Excision Is Essential for the Management of Patients With Breast Implant-Associated

Anaplastic Large-Cell Lymphoma. Journal of clinical oncology : official journal of the American Society of Clinical Oncology 2016;34:160-8.
65. Clemens MW, Jacobsen ED , Horwitz SM. 2019 NCCN Consensus Guidelines on the Diagnosis and Treatment of Breast Implant-Associated Anaplastic Large Cell Lymphoma (BIA-ALCL). Aesthetic Surgery Journal 2019;39:S3-S13.
66. Brown RA, Fernandez-Pol S , Kim J. Primary cutaneous anaplastic large cell lymphoma. Journal of cutaneous pathology 2017;44:570-7.
67. Cocks M, Porcu P, Wick MR , Gru AA. Recent Advances in Cutaneous T-cell Lymphoma: Diagnostic and Prognostic Considerations. Surg Pathol Clin 2019;12:783-803.
68. Kartan S, Johnson WT, Sokol K, Alpdogan O, Gru AA, Nikbakht N et al. The spectrum of CD30+ T cell lymphoproliferative disorders in the skin. Chinese clinical oncology 2019;8:3.
69. Stein H, Foss HD, Durkop H, Marafioti T, Delsol G, Pulford K et al. CD30(+) anaplastic large cell lymphoma: a review of its histopathologic, genetic, and clinical features. Blood 2000;96:3681-95.
70. Massone C , Cerroni L. Phenotypic Variability in Primary Cutaneous Anaplastic Large T-cell Lymphoma: A Study on 35 Patients. The American Journal of dermatopathology 2014;36.
71. Felgar RE, Macon WR, Kinney MC, Roberts S, Pasha T , Salhany KE. TIA-1 expression in lymphoid neoplasms. Identification of subsets with cytotoxic T lymphocyte or natural killer cell differentiation. The American journal of pathology 1997;150:1893-900.
72. Hosoi M, Ichikawa M, Imai Y , Kurokawa M. A case of anaplastic large cell lymphoma, ALK positive, primary presented in the skin and relapsed with systemic involvement and leukocytosis after years of follow-up period. International journal of hematology 2010;92:667-8.
73. Gonzalez CL, Medeiros LJ, Braziel RM , Jaffe ES. T-cell lymphoma involving subcutaneous tissue: A clinicopathologic entity commonly associated with hemophagocytic syndrome. American Journal of Surgical Pathology 1991;15:17-27.
74. López-Lerma I, Peñate Y, Gallardo F, Martí RM, Mitxelena J, Bielsa I et al. Subcutaneous panniculitis-like T-cell lymphoma: Clinical features, therapeutic approach, and outcome in a case series of 16 patients. Journal of the American Academy of Dermatology 2018;79:892-8.
75. Willemze R, Jansen PM, Cerroni L, Berti E, Santucci M, Assaf C et al. Subcutaneous panniculitis-like T-cell lymphoma: definition, classification, and prognostic factors: an EORTC Cutaneous Lymphoma Group Study of 83 cases. Blood 2008;111:838-45.
76. Gallardo F , Pujol RM. Subcutaneous Panniculitic-Like T-Cell Lymphoma and Other Primary Cutaneous Lymphomas with Prominent Subcutaneous Tissue Involvement. Dermatologic Clinics 2008;26:529-40.
77. Lopez-Lerma I, Penate Y, Gallardo F, Marti RM, Mitxelena J, Bielsa I et al. Subcutaneous panniculitis-like T-cell lymphoma: Clinical features, therapeutic approach, and outcome in a case series of 16 patients. J Am Acad Dermatol 2018;79:892-8.
78. Kim JS, Jeong YJ, Sohn MH, Jeong HJ, Lim ST, Kim DW et al. Usefulness of F-18 FDG PET/CT in subcutaneous panniculitis-like T cell lymphoma: Disease extent and treatment response evaluation. Radiology and Oncology 2012;46:279-83.
79. Lester L, Ewalt M, Warnke R , Kim J. Systemic panniculitis-like T-cell lymphoma with involvement of mesenteric fat and subcutis. Journal of cutaneous pathology 2015;42:46-9.
80. Ohtsuka M, Miura T , Yamamoto T. Clinical characteristics, differential diagnosis, and treatment outcome of subcutaneous panniculitis-like T-cell lymphoma: A literature review of published Japanese cases. European Journal of Dermatology 2017;27:34-41.

81. Michonneau D, Petrella T, Ortonne N, Ingen-Housz-Oro S, Franck N, Barete S et al. Subcutaneous panniculitis-like T-cell lymphoma: Immunosuppressive drugs induce better response than polychemotherapy. Acta Dermato-Venereologica 2017;97:358-64.
82. Weenig RH, Ng CS , Perniciaro C. Subcutaneous panniculitis-like T-cell lymphoma: an elusive case presenting as lipomembranous panniculitis and a review of 72 cases in the literature. Am J Dermatopathol 2001;23:206-15.
83. Massone C, Chott A, Metze D, Kerl K, Citarella L, Vale E et al. Subcutaneous, blastic natural killer (NK), NK/T-cell, and other cytotoxic lymphomas of the skin: a morphologic, immunophenotypic, and molecular study of 50 patients. The American journal of surgical pathology 2004;28:719-35.
84. Hoque SR, Child FJ, Whittaker SJ, Ferreira S, Orchard G, Jenner K et al. Subcutaneous panniculitis-like T-cell lymphoma: a clinicopathological, immunophenotypic and molecular analysis of six patients. The British journal of dermatology 2003;148:516-25.
85. Parveen Z , Thompson K. Subcutaneous panniculitis-like T-cell lymphoma: redefinition of diagnostic criteria in the recent World Health Organization-European Organization for Research and Treatment of Cancer classification for cutaneous lymphomas. Archives of pathology & laboratory medicine 2009;133:303-8.
86. Gayden T, Sepulveda FE, Khuong-Quang D-A, Pratt J, Valera ET, Garrigue A et al. Germline HAVCR2 mutations altering TIM-3 characterize subcutaneous panniculitis-like T cell lymphomas with hemophagocytic lymphohistiocytic syndrome. Nature Genetics 2018;50:1650-7.
87. Magro CM, Crowson AN, Kovatich AJ , Burns F. Lupus profundus, indeterminate lymphocytic lobular panniculitis and subcutaneous T-cell lymphoma: a spectrum of subcuticular T-cell lymphoid dyscrasia. Journal of cutaneous pathology 2001;28:235-47.
88. Ma L, Bandarchi B , Glusac EJ. Fatal subcutaneous panniculitis-like T-cell lymphoma with interface change and dermal mucin, a dead ringer for lupus erythematosus. Journal of cutaneous pathology 2005;32:360-5.
89. Park HS, Choi JW, Kim BK , Cho KH. Lupus erythematosus panniculitis: clinicopathological, immunophenotypic, and molecular studies. The American Journal of dermatopathology 2010;32:24-30.
90. Geller S, Myskowski PL, Pulitzer M, Horwitz SM , Moskowitz AJ. Cutaneous T-cell lymphoma (CTCL), rare subtypes: five case presentations and review of the literature. Chinese clinical oncology 2019;8:5.
91. Liau J-Y, Chuang S-S, Chu C-Y, Ku W-H, Tsai J-H , Shih T-F. The presence of clusters of plasmacytoid dendritic cells is a helpful feature for differentiating lupus panniculitis from subcutaneous panniculitis-like T-cell lymphoma. Histopathology 2013;62:1057-66.
92. LeBlanc RE, Tavallaee M, Kim YH , Kim J. Useful Parameters for Distinguishing Subcutaneous Panniculitis-like T-Cell Lymphoma From Lupus Erythematosus Panniculitis. The American journal of surgical pathology 2016;40:745-54.
93. Gru AA, Wick MR , Eid M. Primary cutaneous CD4+ small/medium T-cell lymphoproliferative disorder-clinical and histopathologic features, differential diagnosis, and treatment. Seminars in cutaneous medicine and surgery 2018;37:39-48.
94. Grogg KL, Jung S, Erickson LA, McClure RF , Dogan A. Primary cutaneous CD4-positive small/medium-sized pleomorphic T-cell lymphoma: a clonal T-cell lymphoproliferative disorder with indolent behavior. Modern pathology : an official journal of the United States and Canadian Academy of Pathology, Inc 2008;21:708-15.

728 95. Garcia-Herrera A, Colomo L, Camos M, Carreras J, Balague O, Martinez A et al. Primary
729 cutaneous small/medium CD4+ T-cell lymphomas: a heterogeneous group of tumors with
730 different clinicopathologic features and outcome. Journal of clinical oncology : official journal of
731 the American Society of Clinical Oncology 2008;26:3364-71.
732 96. Yuan Z, Grass GD, Robinson TJ , Kim S. Management of primary cutaneous CD4+ small
733 and medium pleomorphic T-cell lymphoma: A retrospective study. Journal of the American
734 Academy of Dermatology 2018;79:772-4.
735 97. Alberti-Violetti S, Torres-Cabala CA, Talpur R, Corti L, Fanoni D, Venegoni L et al.
736 Clinicopathological and molecular study of primary cutaneous CD4+ small/medium-sized
737 pleomorphic T-cell lymphoma. Journal of cutaneous pathology 2016;43:1121-30.
738 98. Virmani P, Jawed S, Myskowski PL, Horwitz S, Skripnik Lucas A, Moskowitz A et al.
739 Long-term follow-up and management of small and medium-sized CD4(+) T cell lymphoma and
740 CD8(+) lymphoid proliferations of acral sites: a multicenter experience. International journal of
741 dermatology 2016;55:1248-54.
742 99. Beltraminelli H, Leinweber B, Kerl H , Cerroni L. Primary cutaneous CD4+ small-/medium-
743 sized pleomorphic T-cell lymphoma: a cutaneous nodular proliferation of pleomorphic T
744 lymphocytes of undetermined significance? A study of 136 cases. The American Journal of
745 dermatopathology 2009;31:317-22.
746 100. Baum CL, Link BK, Neppalli VT, Swick BL , Liu V. Reappraisal of the provisional entity
747 primary cutaneous CD4+ small/medium pleomorphic T-cell lymphoma: a series of 10 adult and
748 pediatric patients and review of the literature. J Am Acad Dermatol 2011;65:739-48.
749 101. Kim H-J, Han J-H , Min SK. Differential diagnosis of primary cutaneous CD4+
750 small/medium T-cell lymphoproliferative lesions: A report of three cases. Blood Res
751 2017;52:326-9.
752 102. Bekkenk MW, Vermeer MH, Jansen PM, van Marion AM, Canninga-van Dijk MR, Kluin
753 PM et al. Peripheral T-cell lymphomas unspecified presenting in the skin: analysis of prognostic
754 factors in a group of 82 patients. Blood 2003;102:2213-9.
755 103. Virmani P, Jawed S, Myskowski PL, Horwitz S, Skripnik Lucas A, Moskowitz A et al.
756 Long-term follow-up and management of small and medium-sized CD4(+) T cell lymphoma and
757 CD8(+) lymphoid proliferations of acral sites: a multicenter experience. Int J Dermatol
758 2016;55:1248-54.
759 104. Maurelli M, Colato C, Gisondi P , Girolomoni G. Primary Cutaneous CD4(+)
760 Small/Medium Pleomorphic T-Cell Lymphoproliferative Disorder: A Case Series. J Cutan Med
761 Surg 2017;21:502-6.
762 105. James E, Sokhn JG, Gibson JF, Carlson K, Subtil A, Girardi M et al. CD4 + primary
763 cutaneous small/medium-sized pleomorphic T-cell lymphoma: a retrospective case series and
764 review of literature. Leukemia & lymphoma 2015;56:951-7.
765 106. Cetinözman F, Jansen PM , Willemze R. Expression of programmed death-1 in primary
766 cutaneous CD4-positive small/medium-sized pleomorphic T-cell lymphoma, cutaneous pseudo-
767 T-cell lymphoma, and other types of cutaneous T-cell lymphoma. The American journal of
768 surgical pathology 2012;36:109-16.
769 107. Rodríguez Pinilla SM, Roncador G, Rodríguez-Peralto JL, Mollejo M, García JF, Montes-
770 Moreno S et al. Primary cutaneous CD4+ small/medium-sized pleomorphic T-cell lymphoma
771 expresses follicular T-cell markers. The American journal of surgical pathology 2009;33:81-90.

108. Petrella T, Maubec E, Cornillet-Lefebvre P, Willemze R, Pluot M, Durlach A et al. Indolent CD8-positive lymphoid proliferation of the ear: a distinct primary cutaneous T-cell lymphoma? The American journal of surgical pathology 2007;31:1887-92.
109. Kluk J, Kai A, Koch D, Taibjee SM, O'Connor S, Persic M et al. Indolent CD8-positive lymphoid proliferation of acral sites: three further cases of a rare entity and an update on a unique patient. Journal of cutaneous pathology 2016;43:125-36.
110. Greenblatt D, Ally M, Child F, Scarisbrick J, Whittaker S, Morris S et al. Indolent CD8(+) lymphoid proliferation of acral sites: a clinicopathologic study of six patients with some atypical features. Journal of cutaneous pathology 2013;40:248-58.
111. Tjahjono LA, Davis MDP, Witzig TE , Comfere NI. Primary Cutaneous Acral CD8+ T-Cell Lymphoma—A Single Center Review of 3 Cases and Recent Literature Review. 2019;41:644-8.
112. Hathuc VM, Hristov AC , Smith LB. Primary Cutaneous Acral CD8+ T-Cell Lymphoma. 2017;141:1469-75.
113. Kempf W, Kazakov DV, Cozzio A, Kamarashev J, Kerl K, Plaza T et al. Primary cutaneous CD8(+) small- to medium-sized lymphoproliferative disorder in extrafacial sites: clinicopathologic features and concept on their classification. The American Journal of dermatopathology 2013;35:159-66.
114. Wobser M, Roth S, Reinartz T, Rosenwald A, Goebeler M , Geissinger E. CD68 expression is a discriminative feature of indolent cutaneous CD8-positive lymphoid proliferation and distinguishes this lymphoma subtype from other CD8-positive cutaneous lymphomas. British Journal of Dermatology 2015;172:1573-80.
115. Hathuc VM, Hristov AC , Smith LB. Primary Cutaneous Acral CD8(+) T-Cell Lymphoma. Arch Pathol Lab Med 2017;141:1469-75.
116. Hathuc VM, Hristov AC , Smith LB. Primary Cutaneous Acral CD8+ T-Cell Lymphoma. Archives of pathology & laboratory medicine 2017;141:1469-75.
117. Guitart J, Martinez-Escala ME, Subtil A, Duvic M, Pulitzer MP, Olsen EA et al. Primary cutaneous aggressive epidermotropic cytotoxic T-cell lymphomas: reappraisal of a provisional entity in the 2016 WHO classification of cutaneous lymphomas. Modern pathology : an official journal of the United States and Canadian Academy of Pathology, Inc 2017;30:761-72.
118. Berti E, Tomasini D, Vermeer MH, Meijer CJ, Alessi E , Willemze R. Primary cutaneous CD8-positive epidermotropic cytotoxic T cell lymphomas. A distinct clinicopathological entity with an aggressive clinical behavior. The American journal of pathology 1999;155:483-92.
119. Robson A, Assaf C, Bagot M, Burg G, Calonje E, Castillo C et al. Aggressive epidermotropic cutaneous CD8+ lymphoma: a cutaneous lymphoma with distinct clinical and pathological features. Report of an EORTC Cutaneous Lymphoma Task Force Workshop. Histopathology 2015;67:425-41.
120. Swerdlow SH, Campo E, Pileri SA, Harris NL, Stein H, Siebert R et al. The 2016 revision of the World Health Organization classification of lymphoid neoplasms. Blood 2016;127:2375-90.
121. Gormley RH, Hess SD, Anand D, Junkins-Hopkins J, Rook AH , Kim EJ. Primary cutaneous aggressive epidermotropic CD8+ T-cell lymphoma. Journal of the American Academy of Dermatology 2010;62:300-7.
122. Agnarsson BA, Vonderheid EC , Kadin ME. Cutaneous T cell lymphoma with suppressor/cytotoxic (CD8) phenotype: Identification of rapidly progressive and chronic subtypes. Journal of the American Academy of Dermatology 1990;22:569-77.

123. Geller S, Pulitzer M , Myskowski PL. Diffuse eruptive ulcerated plaques. International journal of dermatology 2018;57:1055-7.
124. Introcaso CE, Kim EJ, Gardner J, Junkins-Hopkins JM, Vittorio CC , Rook AH. CD8+ epidermotropic cytotoxic T-cell lymphoma with peripheral blood and central nervous system involvement. Archives of dermatology 2008;144:1027-9.
125. Pulitzer M. Cutaneous T-cell Lymphoma. Clin Lab Med 2017;37:527-46.
126. Nofal A, Abdel-Mawla MY, Assaf M , Salah E. Primary cutaneous aggressive epidermotropic CD8+ T-cell lymphoma: proposed diagnostic criteria and therapeutic evaluation. J Am Acad Dermatol 2012;67:748-59.
127. Gormley RH, Hess SD, Anand D, Junkins-Hopkins J, Rook AH , Kim EJ. Primary cutaneous aggressive epidermotropic CD8+ T-cell lymphoma. J Am Acad Dermatol 2010;62:300-7.
128. Guitart J, Martinez-Escala ME, Subtil A, Duvic M, Pulitzer MP, Olsen EA et al. Primary cutaneous aggressive epidermotropic cytotoxic T-cell lymphomas: reappraisal of a provisional entity in the 2016 WHO classification of cutaneous lymphomas. Modern pathology : an official journal of the United States and Canadian Academy of Pathology, Inc 2017;30:761-72.
129. Geller S, Myskowski PL , Pulitzer M. NK/T-cell lymphoma, nasal type, γδ T-cell lymphoma, and CD8-positive epidermotropic T-cell lymphoma-clinical and histopathologic features, differential diagnosis, and treatment. Seminars in cutaneous medicine and surgery 2018;37:30-8.
130. Guitart J, Weisenburger DD, Subtil A, Kim E, Wood G, Duvic M et al. Cutaneous γδ T-cell lymphomas: a spectrum of presentations with overlap with other cytotoxic lymphomas. The American journal of surgical pathology 2012;36:1656-65.
131. Toro JR, Liewehr DJ, Pabby N, Sorbara L, Raffeld M, Steinberg SM et al. Gamma-delta T-cell phenotype is associated with significantly decreased survival in cutaneous T-cell lymphoma. Blood 2003;101:3407-12.
132. Toro JR, Beaty M, Sorbara L, Turner ML, White J, Kingma DW et al. γδ T-Cell Lymphoma of the Skin: A Clinical, Microscopic, and Molecular Study. Archives of dermatology 2000;136:1024-32.
133. Guitart J, Weisenburger DD, Subtil A, Kim E, Wood G, Duvic M et al. Cutaneous gammadelta T-cell lymphomas: a spectrum of presentations with overlap with other cytotoxic lymphomas. The American journal of surgical pathology 2012;36:1656-65.
134. Tripodo C, Iannitto E, Florena AM, Pucillo CE, Piccaluga PP, Franco V et al. Gamma-delta T-cell lymphomas. Nature reviews Clinical oncology 2009;6:707-17.
135. Lee DE, Martinez-Escala ME, Serrano LM, Zhou XA, Kaplan JB, Pro B et al. Hemophagocytic Lymphohistiocytosis in Cutaneous T-Cell Lymphoma. JAMA dermatology 2018;154:828-31.
136. Guitart J , Martinez-Escala ME. gammadelta T-cell in cutaneous and subcutaneous lymphoid infiltrates: malignant or not? Journal of cutaneous pathology 2016;43:1242-4.
137. de Wolf-Peeters C , Achten R. gammadelta T-cell lymphomas: a homogeneous entity? Histopathology 2000;36:294-305.
138. Berti E, Cerri A, Cavicchini S, Delia D, Soligo D, Alessi E et al. Primary cutaneous gamma/delta T-cell lymphoma presenting as disseminated pagetoid reticulosis. J Invest Dermatol 1991;96:718-23.
139. Foppoli M , Ferreri AJ. Gamma-delta t-cell lymphomas. European journal of haematology 2015;94:206-18.

140. Toro JR, Beaty M, Sorbara L, Turner ML, White J, Kingma DW et al. gamma delta T-cell lymphoma of the skin: a clinical, microscopic, and molecular study. Arch Dermatol 2000;136:1024-32.
141. Daniels J, Doukas PG, Escala MEM, Ringbloom KG, Shih DJH, Yang J et al. Cellular origins and genetic landscape of cutaneous gamma delta T cell lymphomas. Nat Commun 2020;11:1806.
142. Merrill ED, Agbay R, Miranda RN, Aung PP, Tetzlaff MT, Young KH et al. Primary Cutaneous T-Cell Lymphomas Showing Gamma-Delta (γδ) Phenotype and Predominantly Epidermotropic Pattern are Clinicopathologically Distinct From Classic Primary Cutaneous γδ T-Cell Lymphomas. The American journal of surgical pathology 2017;41:204-15.
143. Matutes E, Brito-Babapulle V, Swansbury J, Ellis J, Morilla R, Dearden C et al. Clinical and laboratory features of 78 cases of T-prolymphocytic leukemia. Blood 1991;78:3269-74.
144. Au WY, Ma SY, Chim CS, Choy C, Loong F, Lie AK et al. Clinicopathologic features and treatment outcome of mature T-cell and natural killer-cell lymphomas diagnosed according to the World Health Organization classification scheme: a single center experience of 10 years. Annals of oncology : official journal of the European Society for Medical Oncology 2005;16:206-14.
145. Au WY, Weisenburger DD, Intragumtornchai T, Nakamura S, Kim WS, Sng I et al. Clinical differences between nasal and extranasal natural killer/T-cell lymphoma: a study of 136 cases from the International Peripheral T-Cell Lymphoma Project. Blood 2009;113:3931-7.
146. Barrionuevo C, Zaharia M, Martinez MT, Taxa L, Misad O, Moscol A et al. Extranodal NK/T-cell lymphoma, nasal type: study of clinicopathologic and prognosis factors in a series of 78 cases from Peru. Applied immunohistochemistry & molecular morphology : AIMM 2007;15:38-44.
147. Chihara D, Ito H, Matsuda T, Shibata A, Katsumi A, Nakamura S et al. Differences in incidence and trends of haematological malignancies in Japan and the United States. British journal of haematology 2014;164:536-45.
148. Laurini JA, Perry AM, Boilesen E, Diebold J, Maclennan KA, Müller-Hermelink HK et al. Classification of non-Hodgkin lymphoma in Central and South America: a review of 1028 cases. Blood 2012;120:4795-801.
149. Li CC, Tien HF, Tang JL, Yao M, Chen YC, Su IJ et al. Treatment outcome and pattern of failure in 77 patients with sinonasal natural killer/T-cell or T-cell lymphoma. Cancer 2004;100:366-75.
150. Liang R. Advances in the management and monitoring of extranodal NK/T-cell lymphoma, nasal type. British journal of haematology 2009;147:13-21.
151. Haverkos BM, Pan Z, Gru AA, Freud AG, Rabinovitch R, Xu-Welliver M et al. Extranodal NK/T Cell Lymphoma, Nasal Type (ENKTL-NT): An Update on Epidemiology, Clinical Presentation, and Natural History in North American and European Cases. Current hematologic malignancy reports 2016;11:514-27.
152. Kimura H , Fujiwara S. Overview of EBV-Associated T/NK-Cell Lymphoproliferative Diseases. Frontiers in Pediatrics 2019;6.
153. Arai A, Imadome K-I, Watanabe Y, Yoshimori M, Koyama T, Kawaguchi T et al. Clinical features of adult-onset chronic active Epstein–Barr virus infection: a retrospective analysis. International journal of hematology 2011;93:602-9.
154. Keisuke K, Hiroaki M, Takaharu S, Yasuji K, Koji K, Masaharu M et al. A distinct subtype of Epstein-Barr virus-positive T/NK-cell lymphoproliferative disorder: adult patients with chronic active Epstein-Barr virus infection-like features. Haematologica 2018;103:1018-28.

155. Marchetti MA, Pulitzer MP, Myskowski PL, Dusza SW, Lunning MA, Horwitz SM et al. Cutaneous manifestations of human T-cell lymphotrophic virus type-1-associated adult T-cell leukemia/lymphoma: A single-center, retrospective study. Journal of the American Academy of Dermatology 2015;72:293-301.e2.
156. Mahieux R , Gessain A. HTLV-1 and associated adult T-cell leukemia/lymphoma. Rev Clin Exp Hematol 2003;7:336-61.
157. de Leval L, Rickman DS, Thielen C, Reynies A, Huang YL, Delsol G et al. The gene expression profile of nodal peripheral T-cell lymphoma demonstrates a molecular link between angioimmunoblastic T-cell lymphoma (AITL) and follicular helper T (TFH) cells. Blood 2007;109:4952-63.
158. Grogg KL, Attygalle AD, Macon WR, Remstein ED, Kurtin PJ , Dogan A. Angioimmunoblastic T-cell lymphoma: a neoplasm of germinal-center T-helper cells? Blood 2005;106:1501-2.
159. Krenacs L, Schaerli P, Kis G , Bagdi E. Phenotype of neoplastic cells in angioimmunoblastic T-cell lymphoma is consistent with activated follicular B helper T cells. Blood 2006;108:1110-1.
160. Dupuis J, Boye K, Martin N, Copie-Bergman C, Plonquet A, Fabiani B et al. Expression of CXCL13 by Neoplastic Cells in Angioimmunoblastic T-Cell Lymphoma (AITL): A New Diagnostic Marker Providing Evidence That AITL Derives From Follicular Helper T Cells. The American journal of surgical pathology 2006;30.
161. Rüdiger T, Weisenburger DD, Anderson JR, Armitage JO, Diebold J, MacLennan KA et al. Peripheral T-cell lymphoma (excluding anaplastic large-cell lymphoma): results from the Non-Hodgkin's Lymphoma Classification Project. Annals of oncology : official journal of the European Society for Medical Oncology 2002;13:140-9.
162. Botros N, Cerroni L, Shawwa A, Green PJ, Greer W, Pasternak S et al. Cutaneous manifestations of angioimmunoblastic T-cell lymphoma: clinical and pathological characteristics. The American Journal of dermatopathology 2015;37:274-83.
163. Yang QX, Pei XJ, Tian XY, Li Y , Li Z. Secondary cutaneous Epstein-Barr virus-associated diffuse large B-cell lymphoma in a patient with angioimmunoblastic T-cell lymphoma: a case report and review of literature. Diagnostic pathology 2012;7:7.
164. Poon F, Ieremia E, Collins G , Matin RN. Epstein-Barr Virus-Induced Cutaneous Diffuse Large B-Cell Lymphoma in a Patient With Angioimmunoblastic T-Cell Lymphoma. The American Journal of dermatopathology 2019;41:927-30.

Table I. Key Features of CD30+ Lymphoproliferative Disorders

	Lymphomatoid Papulosis	PC Anaplastic Large Cell Lymphoma
Epidemiology	Median age is 5th decade of life	Median age is 6th decade of life
Clinical Features	Clustered or disseminated papules or nodules that regress and recur	Rapidly growing, solitary or localized group of firm, nodule(s) that may ulcerate, tend to be larger than 1cm
	Predilection for trunk and extremities	Predilection for head and neck, and extremities
	Spontaneous regression, frequent cutaneous relapse, skin-limited although association with other lymphoid malignancies (most commonly another primary CTCL)	May spontaneously regress but relapse common, rare extracutaneous dissemination (10-15%) most commonly in regional lymph node
Histologic Features	Varies by subtype (see Table II)	Organized in sheets Large irregular lymphocytes Eosinophilic or amphophilic cytoplasm
Predominant Immunophenotype	CD4+ (Type A,B,C), CD8+ (Type D,E), CD30+	CD30+, CD4+, ALK-, EMA- , CLA+
5-year survival	100%	93% (in early T-stage skin disease)

ALK, anaplastic lymphoma kinase; *CLA*, cutaneous lymphocyte antigen; *EMA*, epithelial membrane antigen; *PC*, primary cutaneous

Table II. Histologic and immuno[boilerplate: Journal Pre-proof]of lymphomatous papulosis subtypes[a].

Subtype	Histologic Features	Predominant Phenotype	Differential Diagnosis	Distinguishing Characteristics
Type A (>80%)	Wedge Shaped Infiltrate Large atypical lymphocytes, scattered or small clusters (<50% infiltrate) Numerous background inflammatory cells (histocytes, neutrophils, eosinophils)	CD4+ / CD8- CD30+	pcALCL	Large solitary or grouped nodules
			MF (Transformed)	Typically tumors (+/- patches and plaques)
			Arthropod bite reaction	Clinical presentation
Type B (<5%)	Epidermotropic infiltrate of small to medium sized lymphocytes Cells with cerebriform nuclei	CD4+ / CD8- CD30+/-	MF (Patch/Plaque)	Patches and plaques
Type C (~10%)	Sheets of large atypical lymphocytes (>50% infiltrate) Few inflammatory cells	CD4+ / CD8- CD30+	pcALCL	Large solitary or grouped nodules
			MF (Transformed)	Typically tumors (+/- patches and plaques)
			Peripheral T-cell lymphoma	Absent or minimal CD30 expression
			ATLL	HTLV-1/2 tumor genome integration
Type D (<5%)	Epidermotropic infiltrate of cytotoxic T-cell like (CD8+) lymphocytes	CD4- / CD8+ CD30+	CD8+ aggressive epidermotropic T-cell lymphoma	Multiple rapidly evolving plaques and nodules
				Necrosis and erosions
			Pagetoid reticulosis/CD8+ MF	Localized or solitary scaly lesions, hypopigmented patches
Type E (<5%)	Perivascular and angioinvasive infiltrates of atypical lymphocytes	CD4- / CD8+ CD30+	Other T-cell lymphomas with perivascular/angioinvasive infiltrates (PTCL, AITL, CD8+ aggressive epidermotropic T-cell lymphoma, cutaneous gamma-delta T-cell lymphoma, ENKTCL)	Variable clinical presentation and other distinguishing histopathologic and immunophenotypic characteristics
6p25.3 rearrangement (<5%)	Localized lesions Biphasic growth pattern Epidermis: small cerebriform lymphocytes, Dermis: larger transformed lymphocytes	CD4+ / CD8- or CD4- / CD8+ CD30+	MF (Transformed)	Typically tumors (+/- patches and plaques)
			pcALCL	Typically presents as large and/or ulcerating masses and progressive (non-regressing) clinical behavior

AITL, angioimmunoblastic T-cell lymphoma*; ATLL*, adult T-cell lymphoma/leukemia *;EBV*, Epstein-Barr virus *; ENKTCL*, extranodal natural killer/T-cell lymphoma*;* HTLV-1, human T-cell lymphotropic virus type 1*; IHC*,immunohistochemistry*;MF*, mycosis fungoides; *pcALCL*, primary cutaneous anaplastic large cell lymphoma; *PTCL*, peripheral T-cell lymphoma; *TCR*, T-cell receptor

a. Partially adapted from Rein Willemze, Lorenzo Cerroni, Werner Kempf, Emilio Berti, Fabio Facchetti, Steven H. Swerdlow, Elaine S. Jaffe; The 2018 update of the WHO-EORTC classification for primary cutaneous lymphomas. Blood 2019

Table III. Key Features of indolent non MF/SS cutaneous T-cell lymphomas

	PCSM-TCLPD	Acral CD8+ TCL	SPTCL
Epidemiology	Median age is 5th decade of life	Median age is 5th decade of life	Median age is 3rd decade of life (Female predominance)
Clinical Features	Solitary erythematous papule, nodule or plaque Predilection for the face, neck or upper trunk	Solitary papule or nodule Predilection for ears, hands, feet, or nose	Multiple subcutaneous, deeply seated, indurated plaques or nodules Predilection for lower extremities and trunk, and less commonly the upper extremities B-symptoms common, association with HPS and autoimmune diseases
Histologic Features	Dermal and sometimes subcutis involvement Small to medium pleomorphic cells Reactive infiltrates of B-cells, plasma cells, and/or histiocytes common	Dermal and sometimes subcutis involvement Bland medium sized cells with irregular nuclei	Invasion of dermis and subcutaneous tissue sparing the epidermis and upper dermis Lobular panniculitis with atypical lymphocyte rimming, fat necrosis, and cytophagocytosis common Small or medium cells with irregular hyperchromatic nuclei
Predominant Immunophenotype	CD3+, CD4+, CD8-, CD30-, and PD-1+ Variable loss of pan-T-cell markers	CD3+, CD4-, CD8+, CD30- Variable loss of pan-T-cell markers	CD3+, CD4-, CD8+, CD56-, βF1+, and TCRγ1-, EBV-
5-year survival	100%	100%	80% (lower with concurrent HPS)

PCSM-TCLPD, Primary cutaneous CD4+ small-medium sized T-cell lymphoproliferative disorder; *SPTCL*, subcutaneous panniculitis-like T-cell lymphoma; *TCL*, T-cell lymphoma;*TCR*, T-cell receptor

Table IV. Key Features of select aggressive cutaneous T-cell lymphomas

	PCAETCL	PCGD-TCL
Epidemiology	Presents in 7th decade of life	Median age is 6th decade of life
Clinical Features	Rapidly progressive, usually disseminated, ulceronecrotic nodules and tumors, or hyperkeratotic patches and plaques May spread to extracutaneous sites; lymph nodes and bone marrow typically spared	Disseminated, rapidly progressing necrotic and ulcerating nodules, tumors and deep plaques Lymph nodes and bone marrow typically spared; B-symptoms common, association with HPS
Histologic Features	Dermal infiltrates Epidermotropism in a pagetoid or linear distribution, epidermal necrosis and ulceration common. Medium sized cells with hyperchromatic round nuclei and coarse chromatin	Invasion of epidermis, dermis, and subcutanous tissue May occur as mild epidermotropism to marked pagetoid reticulosis-like infiltrates, tissue necrosis common Medium or large cells containing course clumped chromatin
Predominant Immunophenotype	CD3+, CD4-, CD8+, CD56- Granzyme B+, perforin+, and TIA-1+ EBV-	CD3+, CD4-, CD8-, βF1-. TCRδ1+ in frozen sections. Granzyme B+, perforin+, and TIA-1+ (variable), CD56+ (variable) EBV-
5-year survival	31%	11%

EBV, Epstein-Barr virus*; HPS*, hemophagocytic syndrome; *NK*, natural killer; *PCAETCL*, primary cutaneous aggressive epidermotropic CD8+ T-cell lymphoma; *PCGD-TCL*, primary cutaneous gamma delta T-cell lymphoma

Figure 1. Lymphomatoid Papulosis. Erythematous papules on upper extremity

Figure 2. Primary cutaneous anaplastic large cell lymphoma. Solitary ulcerated nodule on lower abdomen

Figure 3A. Primary cutaneous anaplastic large cell lymphoma (ALCL). Hematoxylin and eosin, 400x original magnification. Large atypical lymphocytes demonstrate characteristic hallmark features: eccentric reniform, c-shaped and wreath or donut shaped nuclei. Mitoses are easily identified. 3B. ALCL. CD30 immunohistochemistry, 400x original magnification. CD30 labels more than 75% of the atypical cells, enabling the diagnosis.

Figure 4A. Subcutaneous panniculitis-like T-cell lymphoma (SPTCL). Large erythematous to violaceous, indurated plaques on lower extremity 4B. SPTCL. Subcutaneous nodules and plaques on upper arm. Areas of lipoatrophy at sites of treated disease.

Figure 5A. Subcutaneous panniculitis-like T-cell lymphoma (SPTCL). Hematoxylin and eosin, 200x original magnification. Small to medium sized atypical lymphocytes infiltrate the subcutaneous adipose tissue, rimming adipocytes. 5B. SPTCL. CD8 immunohistochemistry, 200x original magnification. The tumoral lymphocytes are classically CD8+.

Figure 6. Primary cutaneous CD4+ small/medium T-cell lymphoproliferative disorder. Solitary erythematous papule on abdomen

Figure 7A. Primary cutaneous CD4+ small/medium T-cell lymphoproliferative disorder (SMPTCL). Hematoxylin and eosin, 20x original magnification, dermal nodular infiltrate of small to medium sized lymphocytes admixed with histiocytes, eosinophils, and plasma cells. 7B. SMPTCL. CD4 immunohistochemistry, 200x original magnification, CD4 immunohistochemistry highlight the lesional T-follicle helper lymphocytes

Figure 8. CD8+ acral T-cell lymphoma. Solitary pink nodule above eyebrow

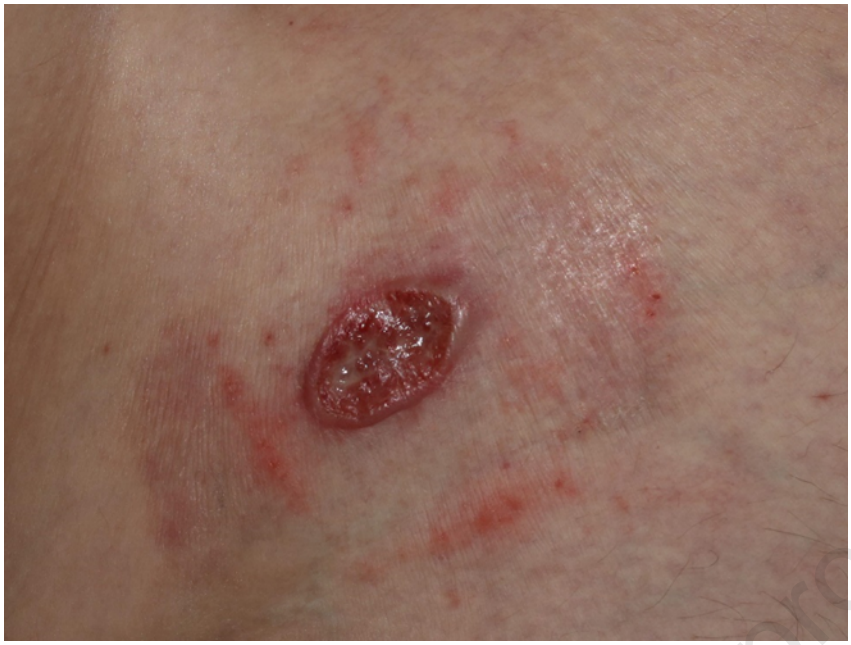
Figure 9. Primary cutaneous CD8+ aggressive epidermotropic cytotoxic T cell lymphoma. Diffuse erythematous plaques on trunk and upper extremities, some with ulceration and crusting.

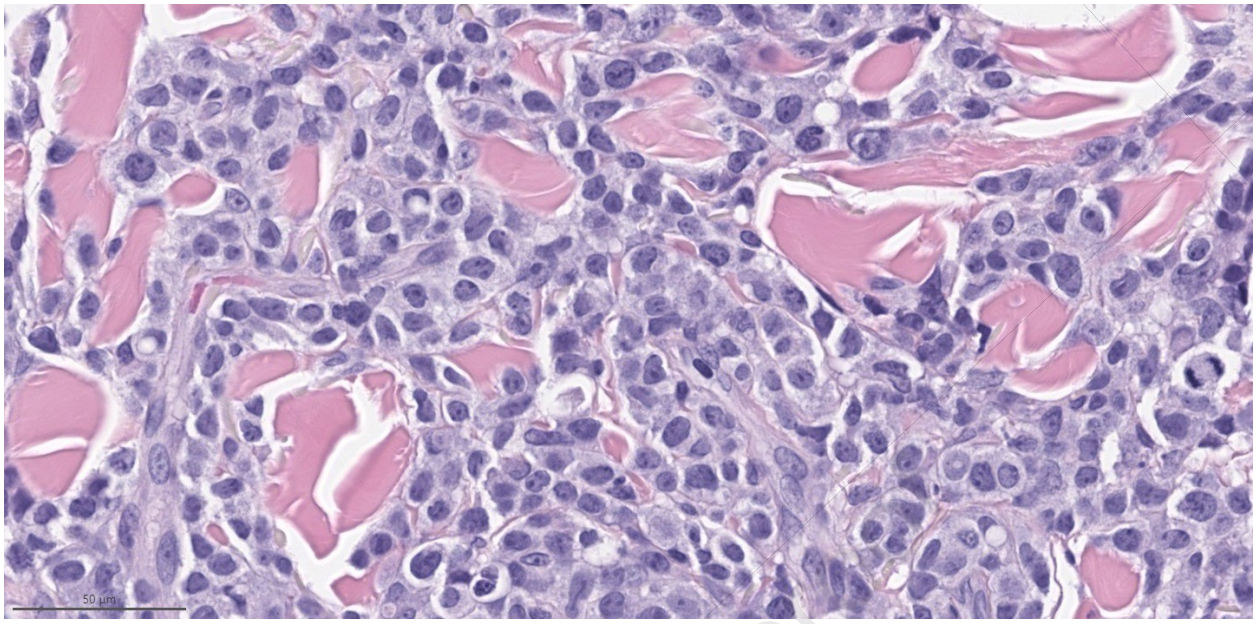
Figure 10. Primary cutaneous gamma-delta T-cell lymphoma. Erythematous, deep plaques with focal ulceration and necrotic crusting on lower extremities

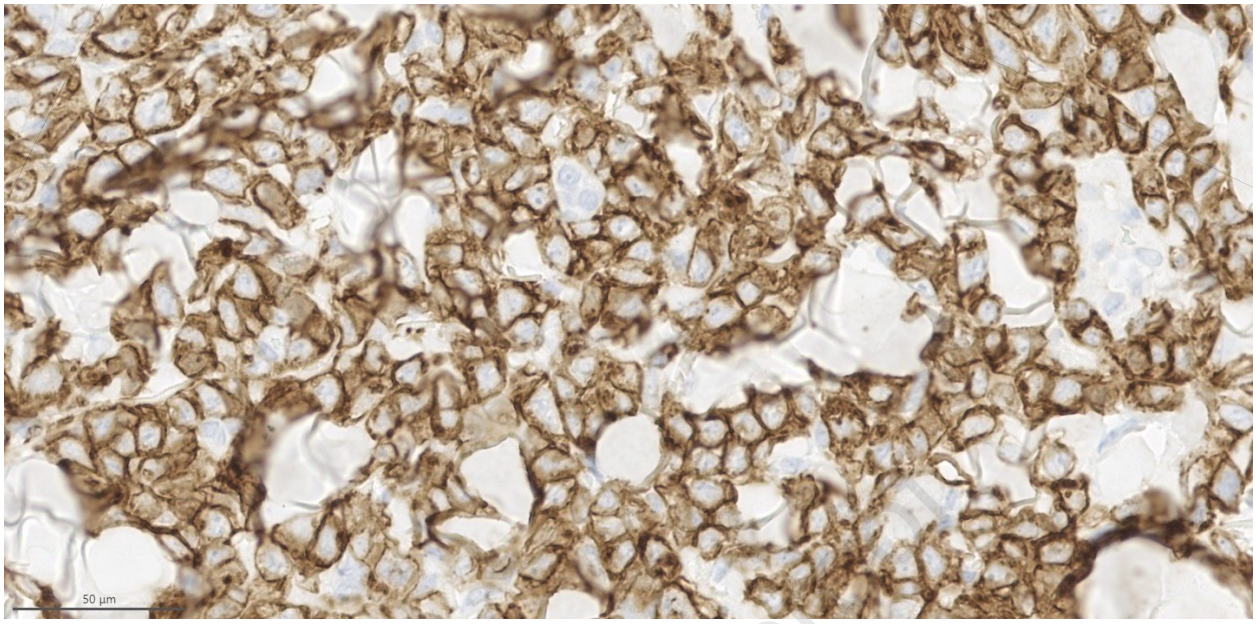
Figure 11A. Primary cutaneous gamma-delta T-cell lymphoma (PCGDTCL). Hematoxylin and eosin, 200x original magnification. Medium to large sized lymphocytes are pleomorphic and hyperchromatic, obscuring normal architecture of epidermal, dermal and subcutaneous structures. 11B. PCGDTCL. TCR-delta immunohistochemistry, 200x original magnification. TCR delta shows > 50% of the infiltrate to be comprised of gamma/delta T-cells.

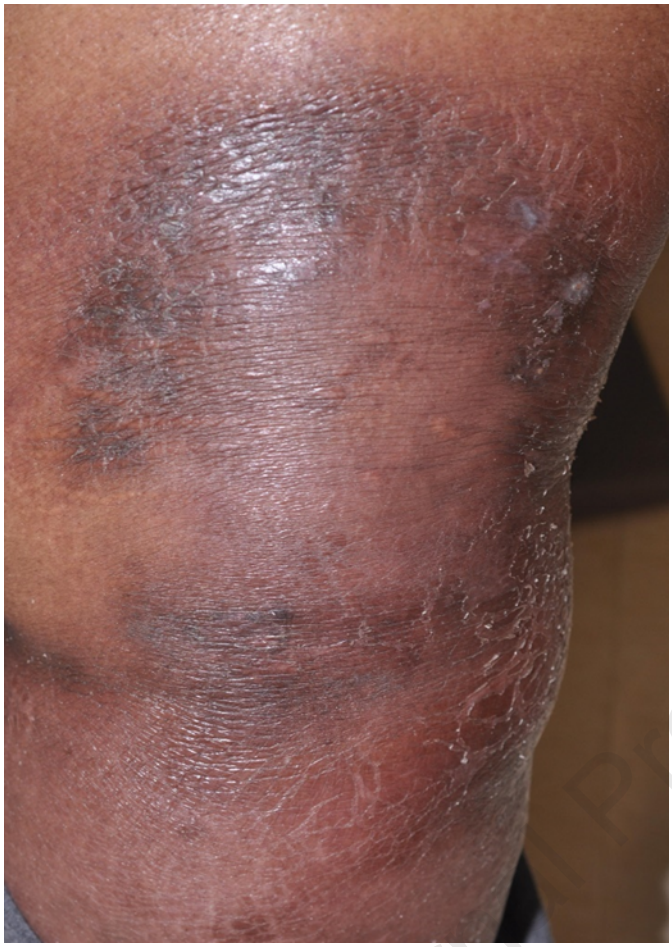
Figure 12A. Adult T-cell leukemia/lymphoma. Pink to tan monomorphic papules coalescing on trunk. 12B. Adult T-cell leukemia/lymphoma. Multiple firm erythematous to violaceous nodules on lower extremities.

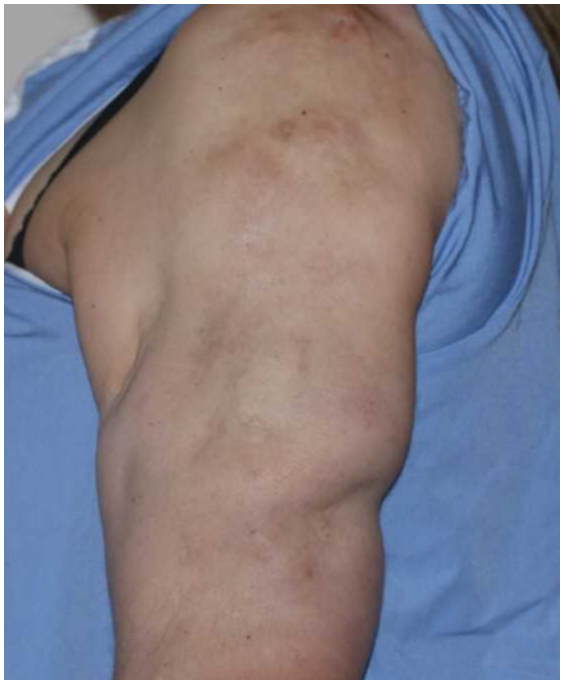
Figure 13. Peripheral T-cell lymphoma not otherwise specified. Erythematous papulonodules on trunk

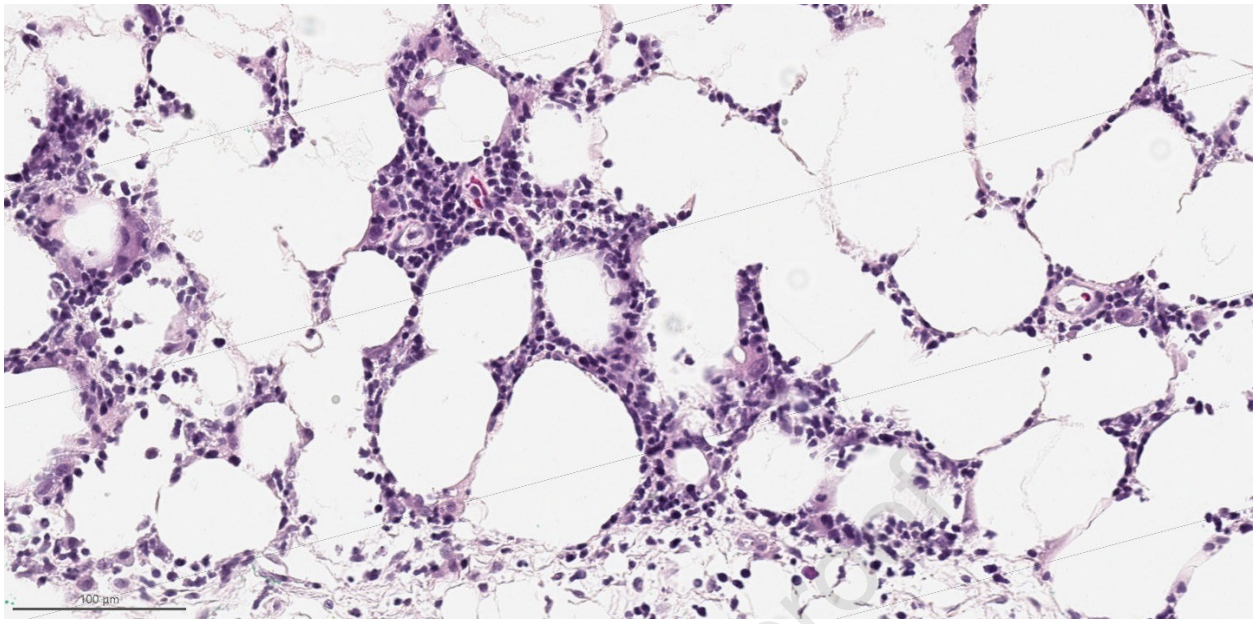


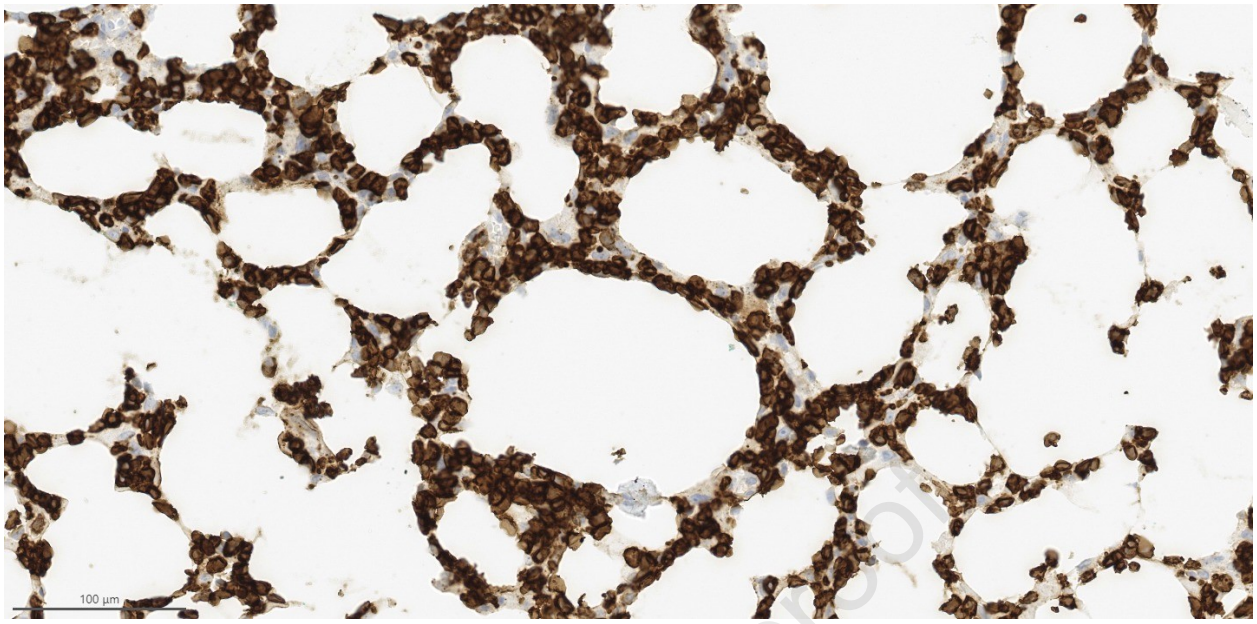


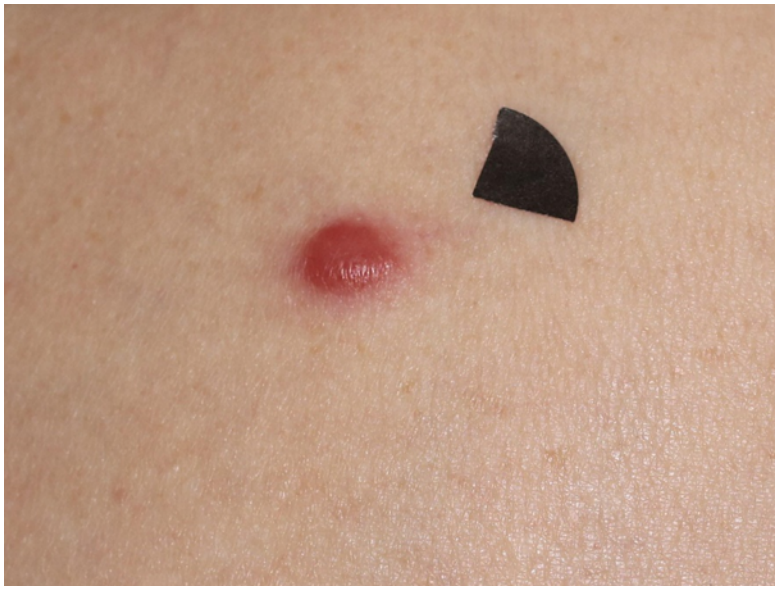


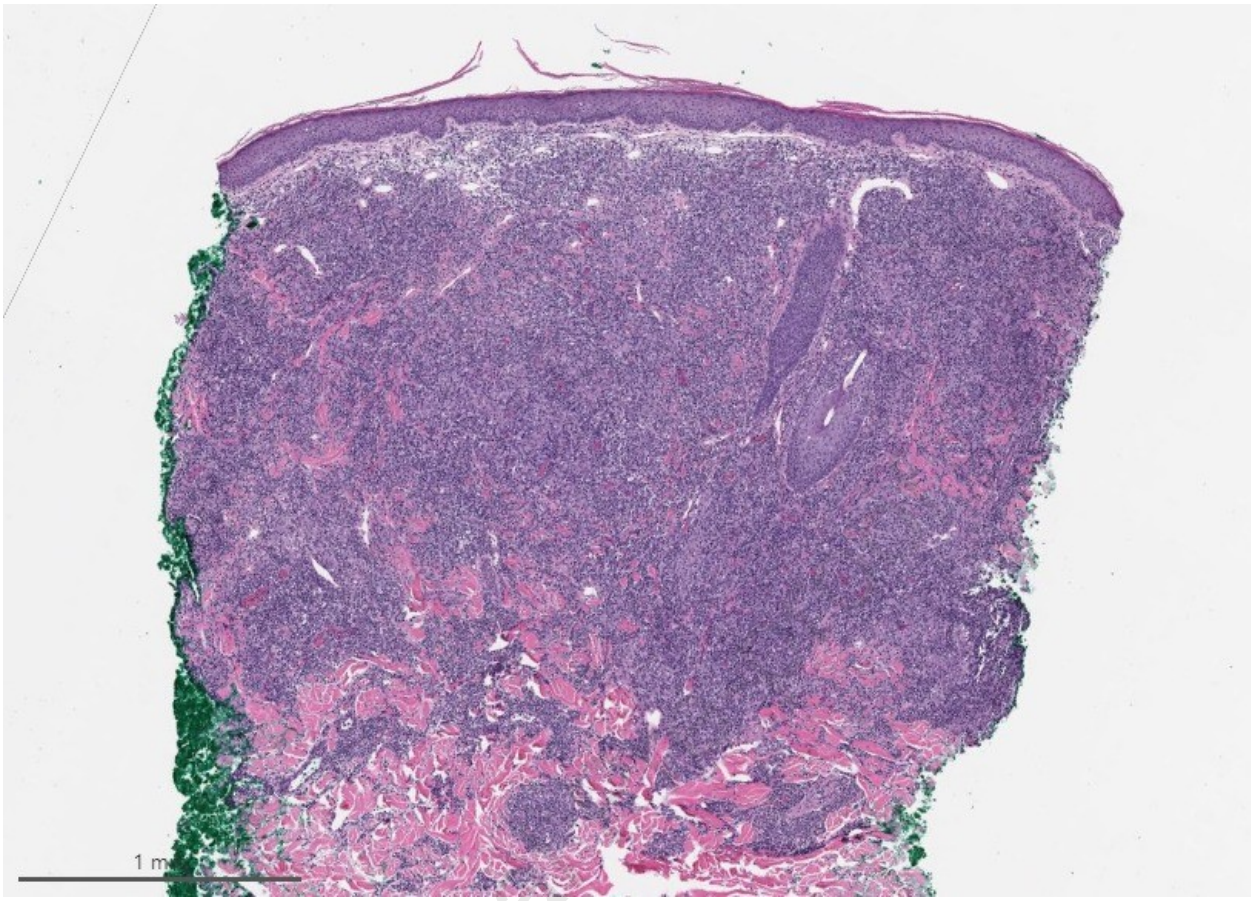


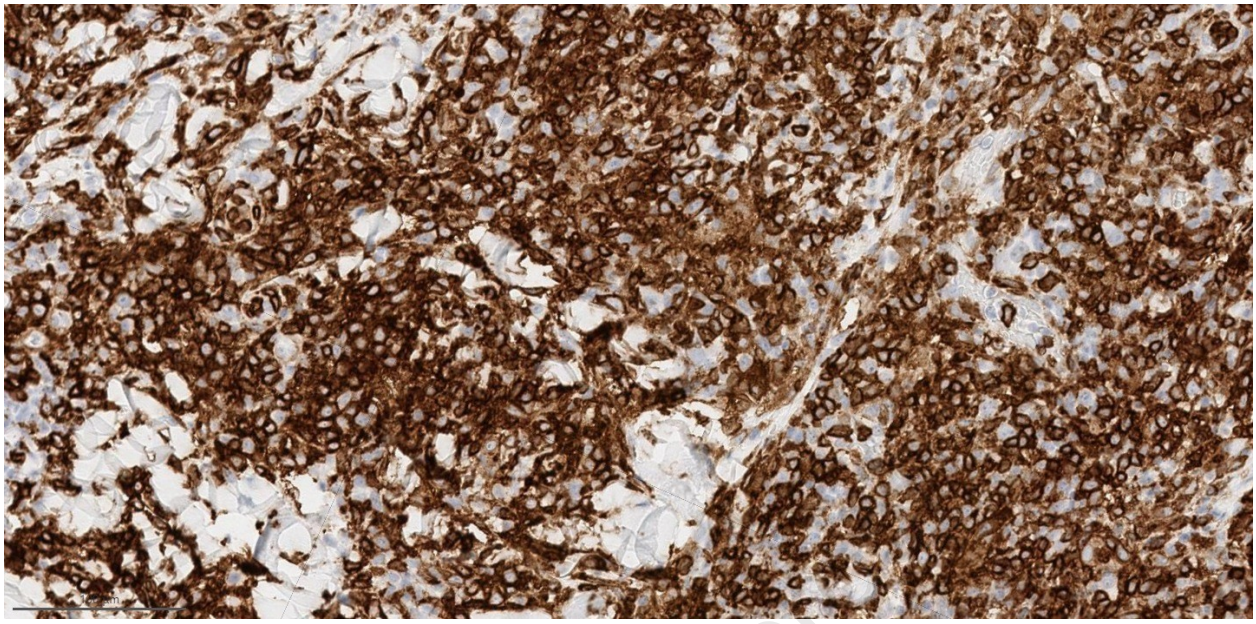


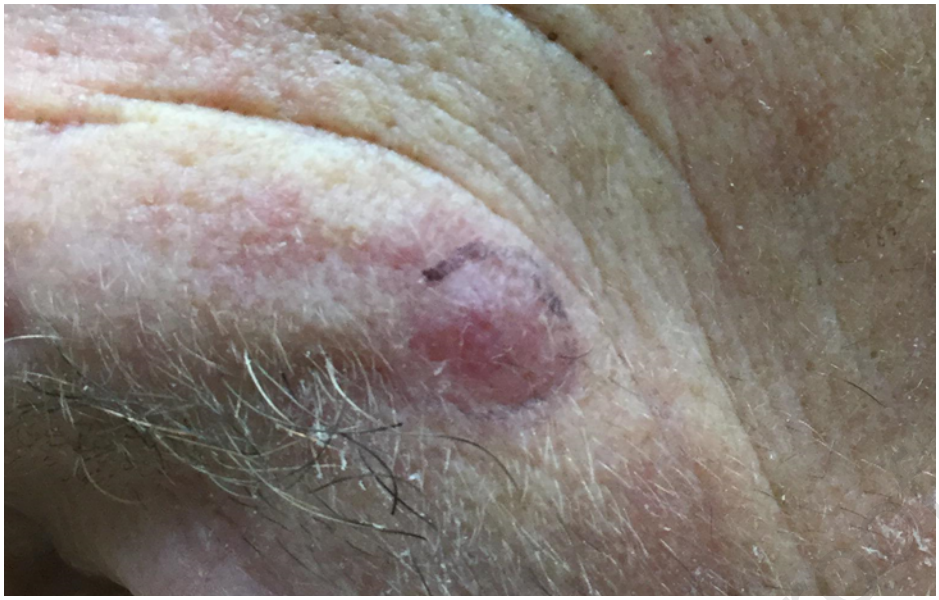


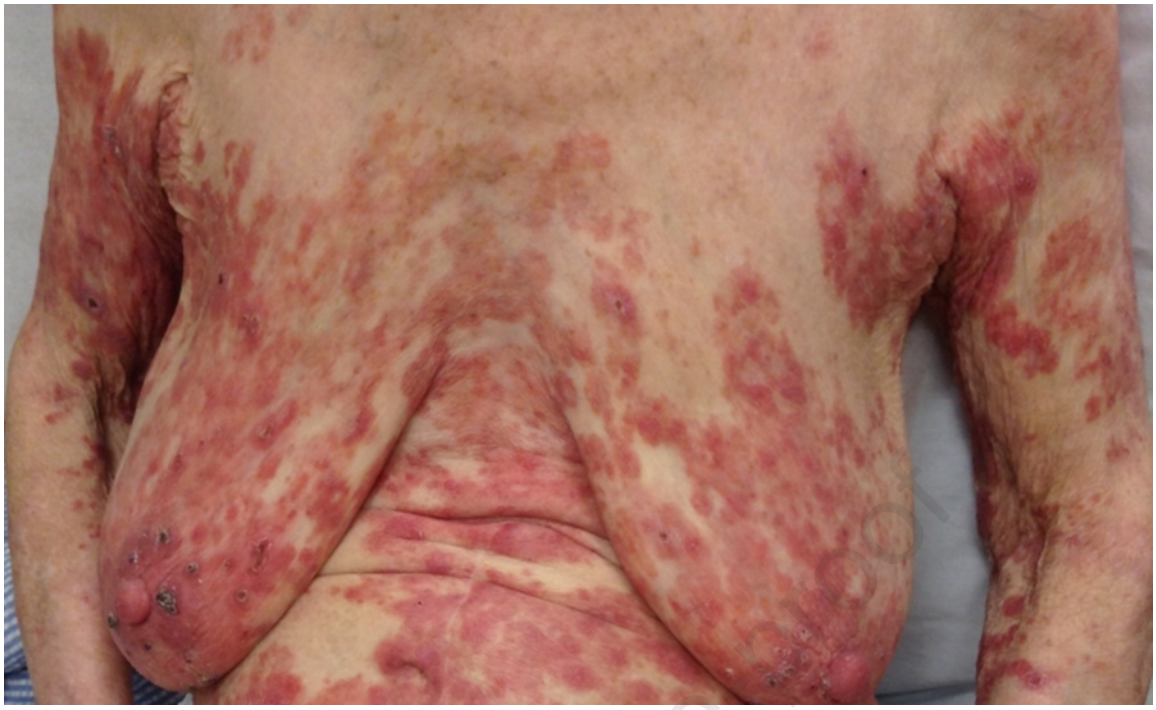


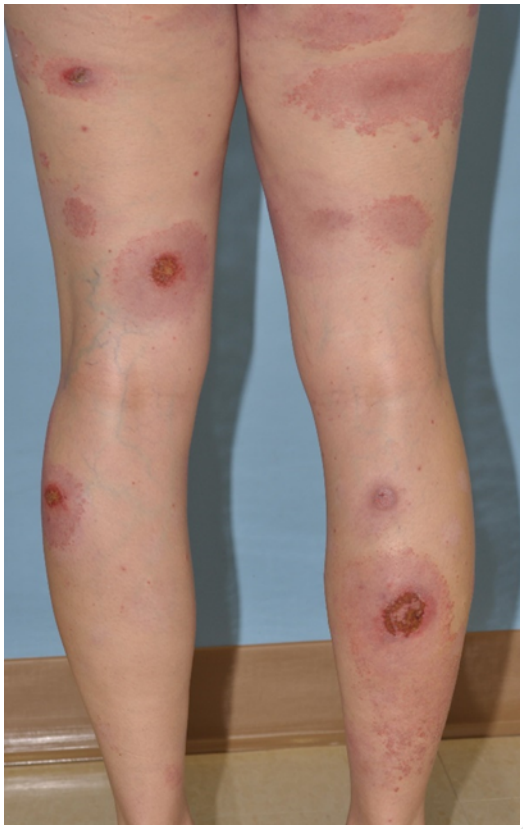


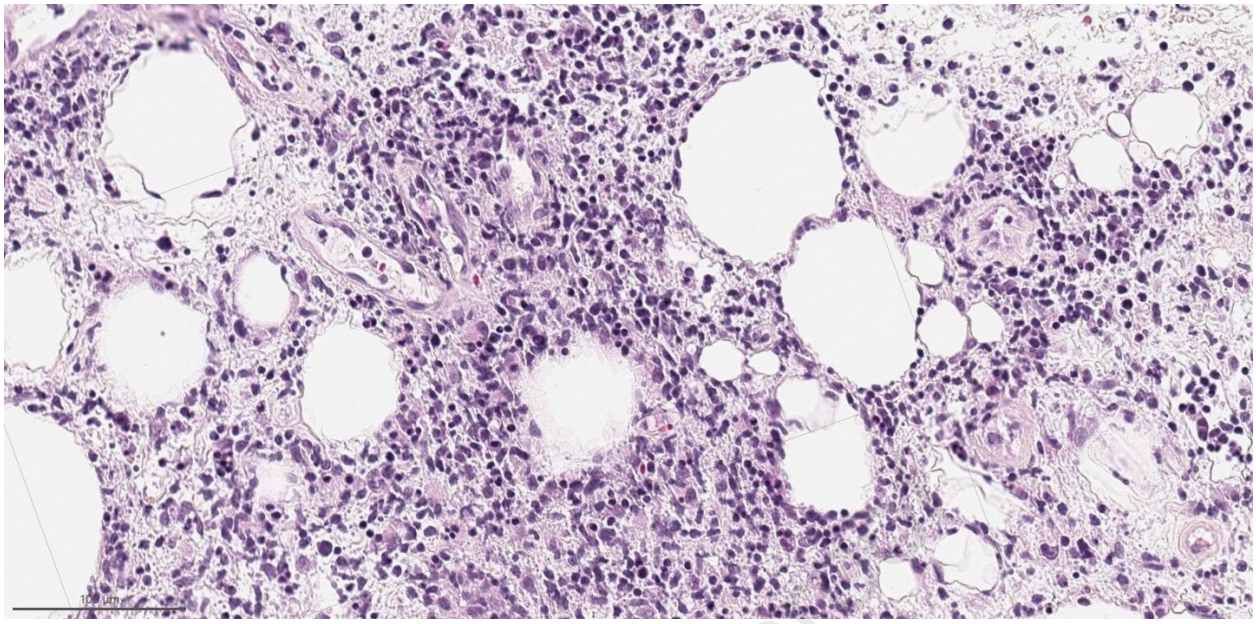


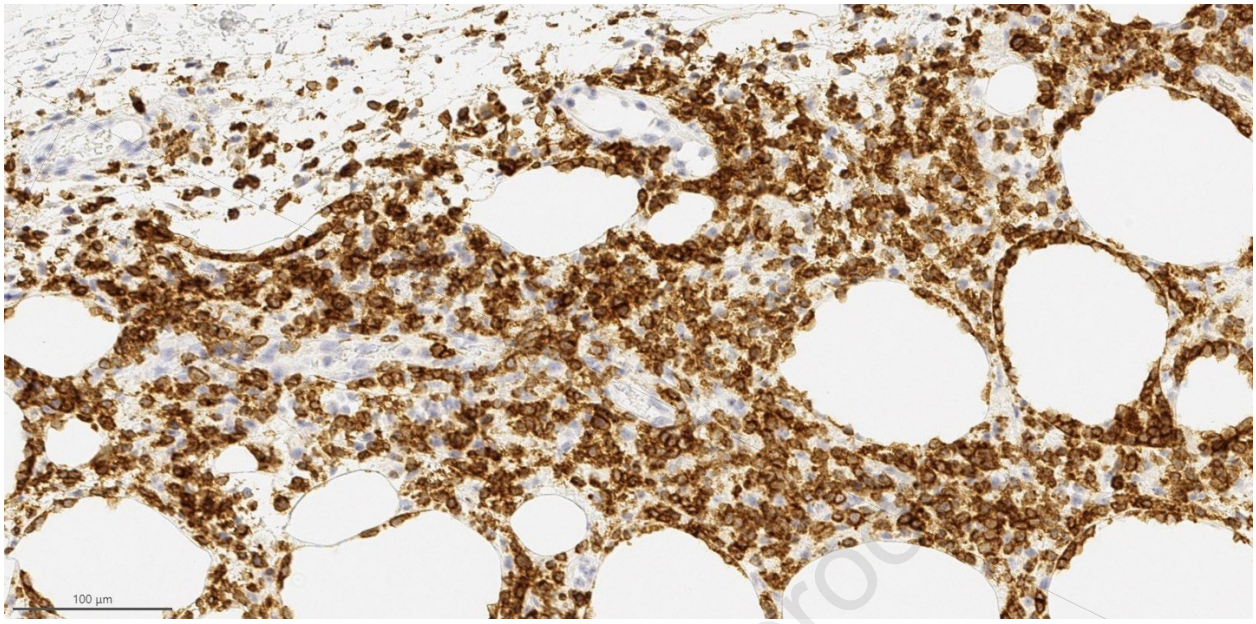


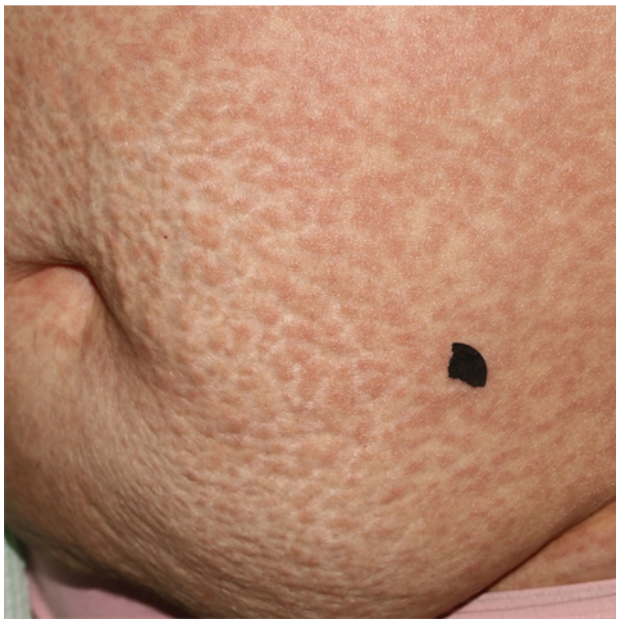


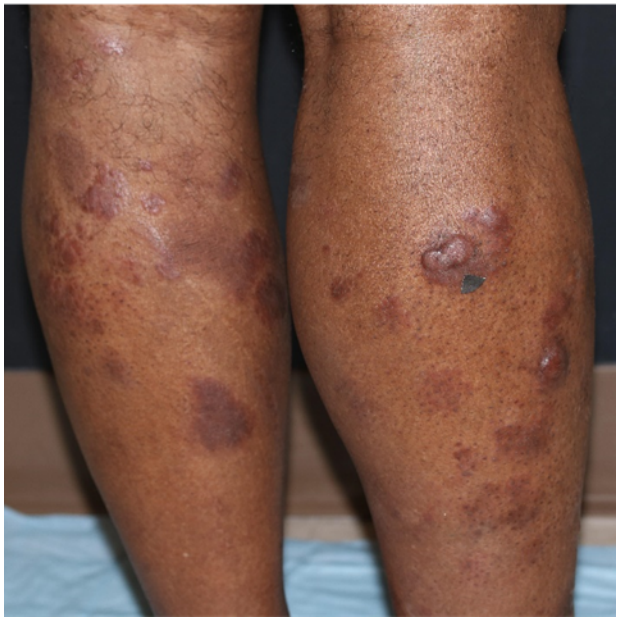


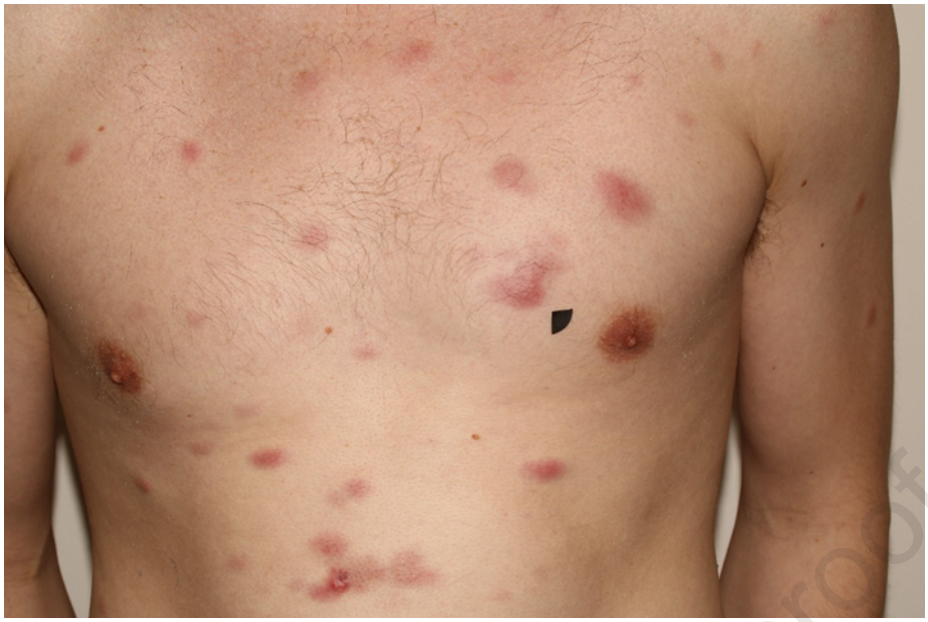


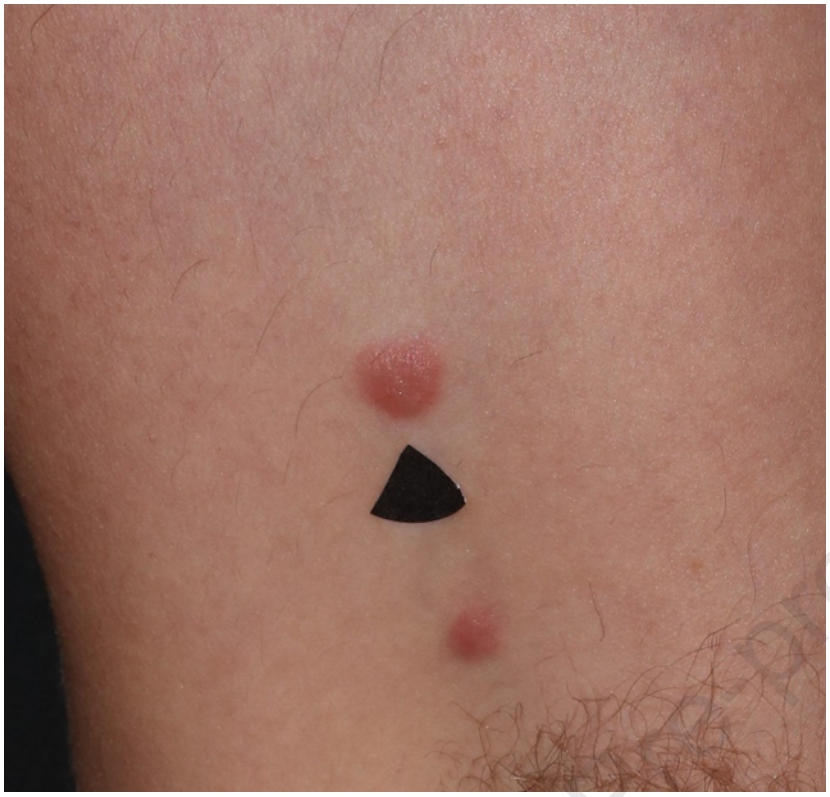












Clinical Features and Differential Diagnosis Key Points

Primary cutaneous CD30+ lymphoproliferative disorders

1. Lymphomatoid papulosis (LyP) typically presents on the trunk or extremities as recurring crops of papules and nodules that resolve over several weeks, with excellent prognosis.
2. The histologic differential diagnosis includes other CD30+ lymphoproliferative disorders, including primary cutaneous anaplastic large cell lymphoma (pcALCL) or transformed MF, or CD30+ reactive inflammatory dermatoses, such as arthropod bites or pityriasis lichenoides.
3. PcALCL presents on the head, neck, and extremities as rapidly growing, solitary or grouped nodules that may ulcerate.
4. Relapses are common and extracutaneous involvement may occur, however limited skin pcALCL has a favorable prognosis (5-year survival rates of 95%)

Subcutaneous panniculitis-like T-cell lymphoma

1. Subcutaneous panniculitis like T-cell lymphoma (SPTCL) presents as subcutaneous, poorly circumscribed, indurated plaques or nodules on the extremities. Systemic B-symptoms are common, and there is an association with autoimmune diseases.
2. The clinical and histologic differential diagnosis includes reactive panniculitides including lupus panniculitis and more aggressive T-cell lymphomas including primary cutaneous gamma delta T-cell lymphoma (PGCD-TCL), although latter often presents with ulcerated lesions.
3. SPTCL has an indolent clinical course with a 5-year survival of 87%, although presence of hemophagocytic syndrome (reported in 7-45% of cases) is associated with poor outcome.

Primary cutaneous CD4+ small/medium T-cell Lymphoproliferative disorder, Primary cutaneous acral CD8+ T-cell lymphoma

1. Primary cutaneous CD4+ small/medium T-cell lymphoproliferative disorder (PCSM-TCL) typically presents as a solitary papule, plaque, or tumor on the head, neck, or upper trunk while primary cutaneous acral CD8+ T-cell lymphoma (acral CD8+ TCL) presents as a solitary papule or nodule localized to the ear or other acral sites including the nose, hands, and feet.
2. The histologic differential diagnosis of acral CD8+ TCL includes other cytotoxic CD8+ CTCL, while the histologic differential diagnosis of PCSM-PTCL includes other T-cell lymphomas with follicular helper phenotype, cutaneous B-cell lymphomas, and pseudolymphoma.
3. PCSM-TCL and acral CD8+ TCL have an excellent prognosis with 5-year survival rate of 100%

Primary cutaneous CD8+ aggressive epidermotropic cytotoxic T cell lymphoma

1. Primary cutaneous CD8+ aggressive epidermotropic cytotoxic T-cell lymphoma (AECTCL) presents as rapidly progressive ulceronecrotic nodules and tumors, or hyperkeratotic patches and plaques that can ulcerate
2. The histologic differential diagnosis includes other CD8+ CTCLs
3. AECTCL is clinically aggressive and has a 5-year survival of 31%.

Primary cutaneous gamma-delta T-cell lymphoma

1. Primary cutaneous gamma-delta T-cell lymphoma (PCGDTCL) typically presents on the extremities as disseminated, rapidly progressing, necrotic and ulcerating nodules, tumors and deep plaques, but scaly plaques that mimic MF and psoriasis may be seen in patients
2. Systemic B-symptoms are common and there is an association with hemophagocytic syndrome
3. PCGDTCL has an aggressive clinical course and poor prognosis (5-year survival of 11%)

Other T-cell lymphomas presenting in the skin

1. Systemic peripheral T-cell lymphomas (PTCLs) are rare, share an aggressive course, and have heterogenous cutaneous manifestations
2. ENKTL (EBV associated) presents as ulcerating plaques or tumors that may extend into the nose, sinuses, or palate, with poor prognosis
3. ATLL (HTLV associated) is subdivided into four subtypes with cutaneous manifestations in 39% to 72% of cases. Skin manifestations include nodulotumoral lesions, maculopapular eruption, plaques, patches, and erythroderma.

Histologic and Immunophenotypic Features Key Points

Primary cutaneous CD30+ lymphoproliferative disorders

1. There are five histologic (A-E) and one genetic WHO (chromosome 6p25.3 rearrangement) recognized subtypes of LyP.
2. Type A is the most common subtype (75-80% of cases) and all subtypes express CD4 except for types D and E which express CD8
3. PALCL consists of nodular dermal infiltrates with at least 75% of cells expressing CD30.
4. Cutaneous lymphocyte antigen (CLA) is typically positive and epithelial membrane antigen (EMA) and anaplastic lymphoma kinase (ALK) is negative in pcALCL, in contrast to sALCL

Subcutaneous panniculitis-like T-cell lymphoma

1. SPTCL consists of a lobular panniculitis, with neoplastic lymphocytes rimming the fat, fat necrosis, and cytophagocytosis.
2. Neoplastic cells express cytotoxic CD8+ phenotype (granzyme, TIA-1, and perforin), and are positive for βF1
3. Cytotoxic phenotype, fat rimming, and erythrophagocytosis are more common in SPTCL over lupus panniculitis, while aggregates of CD123+ plasmacytoid dendritic cells and lymphoid follicles are more characteristic of lupus panniculitis.

Primary cutaneous CD4+ small/medium T-cell LPD, Primary cutaneous acral CD8+ T-cell lymphoma

1. PCSM-TCLPD and acral CD8+ TCL consist of nodular or diffuse infiltrates of small to medium pleomorphic lymphocytes in the dermis.
2. The neoplastic T-cells of PCSM-TCLPD are CD4+/CD8-, with expression of PD-1, BCL6, and CXCL13 suggesting a T-follicular helper phenotype and low Ki67 proliferation index.

Primary cutaneous CD8+ aggressive epidermotropic cytotoxic T cell lymphoma

1. Early papulosquamous lesions are characterized by hyperkeratosis and acanthosis with infiltrates extending to the deep dermis or subcutis in tumor lesions.
2. AECTCL may have pagetoid epidermotropism mimicking MF, and invasion and destruction of the vasculature and adnexal structures is common.
3. Atypical lymphocytes express CD8+ cytotoxic phenotype (granzyme B, perforin, TIA-1) with absent CD56 and EBV expression.

Primary cutaneous gamma-delta T-cell lymphoma

1. PCGDTCL infiltrates the subcutaneous tissue and, unlike SPTCL, frequently involves the epidermis and upper dermis

2. Apoptosis, necrosis, angioinvasion/angiodestruction are frequently observed, and macrophages engulfing lymphocytes can be seen.
3. Cells express either TCR γ or δ and are frequently CD4/CD8 double negative.