Cutaneous CD30-positive T-cell lymphoproliferative disorders—clinical and histopathologic features, differential diagnosis, and treatment

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Abstract

Cutaneous CD30+ T-cell lymphoproliferative disorders (CD30+ LPD) are the second most common form of cutaneous T-cell lymphoma. CD30+ LPD include lymphomatoid papulosis, primary cutaneous anaplastic large-cell lymphoma, and borderline lesions. Despite expression of CD30 by the neoplastic cells as the hallmark of these disorders, they differ in their clinical presentation and histological features as well as the course, the prognosis, and consecutively in the treatment. Diagnosis of CD30+ LPD and distinction from the broad spectrum of differential diagnoses essentially depends on clinicopathologic correlation as well as the results of staging examinations. Although the histological findings indicate a high-grade lymphoma, CD30+ LPD in most cases have a favorable prognosis. Recent advances in targeted therapy have led to new therapeutic approaches to CD30+ LPDs. This review describes the clinicopathologic features of CD30+ LPDs, their differential diagnoses, the treatment, and the role of CD30 as a diagnostic marker and therapeutic target.

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Primary cutaneous CD30+ T-cell lymphoproliferative disorders (CD30+ LPD) account for approximately 30% of primary cutaneous T-cell lymphomas (CTCL), thereby representing the second most common form of CTCL.[1,2] The spectrum of CD30+ LPD encompasses lymphomatoid papulosis (LYP), primary cutaneous anaplastic large-cell lymphoma (PCALCL), and borderline lesions. Their common phenotypic hallmark is the expression of CD30 by the neoplastic cells. CD30 is a cytokine receptor belonging to the tumor necrosis factor receptor superfamily and is involved in the growth control of the tumor cells.[3]

Although LYP, PCALCL, and borderline lesions exhibit overlapping histological and phenotypic features, they significantly differ in their clinical presentation. To distinguish CD30+ LPD from other primary or secondary cutaneous lymphomas, clinicopathologic correlation and staging examination are crucial for the diagnostic work-up.[4,5]

Cutaneous CD30+ LPD exhibit a favorable prognosis in most patients.[4] Therefore, the management of CD30+ T-LPD differs from the treatment modalities applied for systemic CD30+ lymphomas.[5]

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Lymphomatoid papulosis

LYP was first described by Warren L. Macaulay, MD, as a chronic recurrent, self-healing papulonodular skin eruption with histologic features of a malignant lymphoma.[6] Since then, there has been a debate about whether LYP represents a benign lymphoproliferative disorder or whether it should be regarded as a low-grade malignant lymphoma. The etiopathogenesis of LYP is largely unknown. Interaction between CD30 and its ligand appears to play a role in the regression of LYP lesions.[7] LYP may be triggered by external factors such as radiation therapy or immunomodulating drugs such as fingolimid. No oncogenic viruses could consistently be detected in LYP. However, endogenous retroviruses have been identified in tumor cell lines and tumor biopsies of LYP, but their role needs to be elucidated.[8]

Clinical features

LYP usually presents with clusters or disseminated papules and small nodules. Rarely pustular lesions or ulcers can be seen. The individual lesions spontaneously regress within a few weeks or months (Figure 1A). In the angioinavsive LYP type E, rapidly evolving, eschar-like necrotic lesions reaching a diameter of up to 4 cm may develop. Sometimes hypo- or hyperpigmented varioliform scars are left after regression of LYP lesions. The number of lesions varies from only a few to hundreds of lesions. The disease duration is highly variable, from several weeks to years or even decades. LYP mostly occurs in adults, but children may be affected as well.[9] Rare and unusual clinical variants of LYP include acral and other localized forms of LYP. Follicular LYP may present with pustular lesions clinically simulating folliculitis.[10] Papular, self-regressing lesions overlapping with patches of concurrent mycosis fungoides (MF) are referred to as persistent agminated LYP.[11] Oral mucosal involvement in LYP is uncommon.

Histopathologic features

Five histologic variants (A-E) and a distinct genotypic type of LYP with 6p25.3 rearrangement are recognized in the updated 2016 WHO classification.[12] The cardinal features of the different histologic LYP types are given in Table 1. It is noteworthy that various histological types can synchronously be present in an individual patient.[13] Moreover, none of the LYP types has consistently been shown to have any prognostic or therapeutic significance. LYP type A and C are the most common histologic manifestations, accounting for 80% of all LYP biopsies.[4,13] Type A shows a wedge-shaped dermal infiltrate (Figures 1B) of medium-sized to large pleomorphic and anaplastic lymphoid cells, which are scattered or arranged in small clusters in a background of neutrophils, eosinophils, and histiocytes (Figure 1C). Some LYP types, particularly type D and type E, are at a particular risk of being misinterpreted as aggressive lymphomas.[14,15] Additional rare and unusual histopathological

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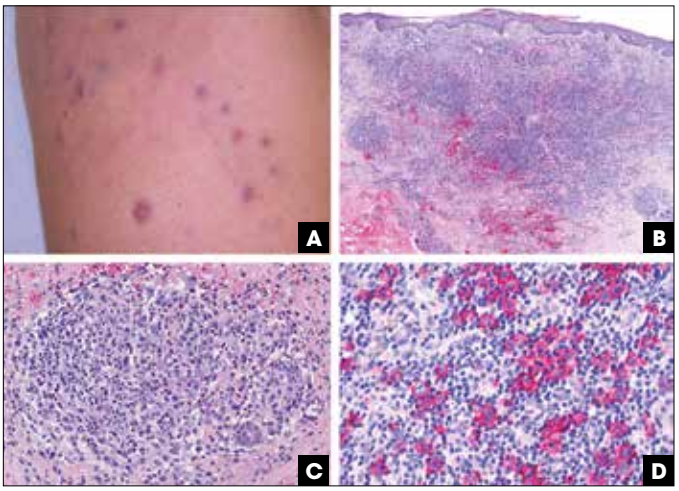

■ **FIGURE 1.** Lymphomatoid papulosis: **(A)** Papulonodular lesions on the right thigh. Individual lesions spontaneously regress within few weeks. **(B)** Wedge-shaped dermal lymphocytic infiltrate (H&E, magnification 2.5x). **(C)** Medium-sized to large lymphoid cells with nuclear pleomorphism with admixed eosinophils and histiocytes (A; H&E, magnification 200x). **(D)** Expression of CD30 by atypical lymphocytes (B; IHC, CD30 stain, magnification 200X). Abbreviations: H&E, hematoxylin–eosin; IHC, immunohistochemistry.

variants of LYP include follicular, syringotropic, granulomatous, and spindle cell LYP (reviewed in reference 10). Because the designation of the different histological types of LYP by alphabetic characters may become confusing, we have proposed an alternative, descriptive terminology.[16]

The atypical lymphoid cells in LYP exhibit the phenotype of activated T helper cells and CD30 (Figure 1D), which is consistently expressed by atypical lymphocytes in all LYP types except for type B, in which variable expression of CD30 is observed. Most commonly, the CD30$^+$ cells express CD4. However, a CD8$^+$ phenotype is observed in all cases of LYP type D (100%), in the majority of LYP type E, and often in children.[9,14,15] The phenotype of the atypical lymphocytes does not have any impact on the course and the prognosis of the disease. Monoclonal rearrangement of T-cell receptor (TCR) genes is detected in 40% to 90% of LYP cases.[17] Because the lack of T-cell clonality does not exclude the diagnosis LYP, molecular studies for clonality are of limited value in the diagnosis of LYP.

Diagnosis

Diagnosis of LYP is based on the characteristic clinical presentation with spontaneous regression of individual tumor lesions within weeks or months as well as the typical histopathological findings. According to international recommendations for the management of CD30$^+$ T-LPD, the recommended laboratory studies include a complete blood cell count with differential, blood chemistry, and lactate dehydrogenase.[5] There is no need for radiologic staging examination or bone marrow biopsy in patients with typical clinical manifestation of LYP, absence of enlarged lymph nodes, and negative blood tests. If physical examination or laboratory tests suggest extracutaneous disease, radiologic staging examinations and biopsy of enlarged lymph nodes are recommended.

Differential diagnosis

The differential diagnosis of LYP is very broad due to the wide histological spectrum of LYP and due to the fact that CD30 expression can be observed in a variety of lymphomas as well as in reactive inflammatory processes such as arthropod bite reactions, drug eruptions, and pityriasis lichenoides (Table 1).[18-20] Each histological LYP type can simulate other cutaneous and aggressive systemic lymphomas (Table 1). As a consequence, clinicopathological correlation and staging are crucial elements in the diagnostic work-up of LYP.[15] It is important to differentiate LYP from secondary cutaneous involvement by systemic anaplastic large-cell lymphoma (ALCL) and to identify underlying immunosuppressive conditions because cutaneous CD30$^+$ LPD arising in immunodeficient patients and systemic ALCL carry a worse prognosis and require treatment with multiagent chemotherapy.

Prognosis

LYP persists usually for several months or years, but is not associated with increased mortality per se.[4,21] Nevertheless, a subset of LYP patients develop a second lymphoid neoplasm, in particular MF, Hodgkin lymphoma (HL), and cutaneous or nodal CD30$^+$ ALCL. These lymphomas are referred to as "LYP-associated malignant lymphomas" and can occur prior to, concurrent with, or after the initial manifestation of LYP. The prevalence of LYP-associated lymphomas reported in the literature varies widely, with a range of none to 62% of LYP patients developing a second lymphoma (reviewed in reference 22). Remarkably, there are only few data on prognostic factors in LYP. Older age, histological types B and C, LYP lesions located on the head, a higher frequency of LYP recurrences, detection of a T-cell clone in the LYP lesions, and expression of fascin by CD30$^+$ cells have been reported as adverse prognostic indicators for the development of LYP-associated lymphomas,[23-25] but these data need to be confirmed by larger studies. Treatment Due to the excellent prognosis, a "wait and see" strategy can be justified, especially because no active therapeutic intervention has so far been proven to alter the course of the disease or to prevent LYP-associated lymphomas.[4,21] For disseminated, numerous, or stigmatizing lesions, ultraviolet light-based therapy or low-dose methotrexate are the first-line therapies.[5] Multiagent chemotherapy should be avoided in LYP. Due to risk for second lymphoid neoplasms, LYP patients should be monitored lifelong so that these potentially fatal LYP-associated lymphomas can be detected early and treated. Recently, brentuximab vedotin (BV) was shown to be effective also in LYP refractory to other treatment modalities,[26,27] although the potential side effects have to be critically balanced again the therapeutic benefit in an indolent lymphoproliferation such as LYP.

Primary cutaneous anaplastic large-cell lymphoma

PCALCL is a primary cutaneous T-cell lymphoma characterized by infiltrates of large T cells with prominent nuclear pleomorphism and expression of CD30 by more than 75% of tumor cells.[1,2] The etiology of PCALCL is unknown. The biology and course of PCALCL significantly differ from systemic ALCL.[28] Remarkably, the rapid growth phase of tumoral lesions and the highly atypi-

TABLE 1 Lymphomatoid papulosis—histological types and differential diagnosis

LyP type	Histology	Differential diagnosis	Distinguishing criteria
Type A	Wedge-shaped infiltrate. Scattered or in small clusters arranged large atypical CD30+ lymphocytes. Admixed histiocytes, eosinophils, neutrophils.	• Mycosis fungoides (transformation) • Hodgkin lymphoma • Arthropod bite reaction	• Patches and plaques in MF versus papulo-nodular lesions in LYP • Staging examination (in nodal HL) • Clinical presentation, pruritus
Type B	Epidermotropic infiltrate of small to medium-sized lymphocytes with variable expression of CD30..	• Mycosis fungoides (patch/plaque stage)	• Patches and plaques in MF versus self-regressing papulo-nodular lesions in LyP
Type C	Nodular cohesive infiltrate of large CD30+ atypical lymphocytes. Only a few reactive cells.	• Anaplastic large-cell lymphoma (primary cutaneous or systemic form) • Mycosis fungoides (transformation) • Peripheral T-cell lymphoma, NOS (primary cutaneous or nodal) • Adult T-cell lymphoma/leukemia	• Clinical presentation with solitary or grouped nodules in pcALCL; staging examinations in sALCL. • Patches and plaques preceding tumors in MF • Lack of CD30 or expression by only a minority of tumor cells; staging examinations • Integration of HTLV-1/2 in tumor cell genome.
Type D	Prominent epidermotropism of atypical lymphocytes with expression of CD8 and CD30.	• Pagetoid reticulosis (PR) • Primary cutaneous aggressive epidermotropic CD8+ cytotoxic TCL	• Localized or solitary erythematous and scaly lesion. • Multiple rapidly evolving plaques and nodules with erosions and necrosis.
Type E	Angioinvasive infiltrates of atypical CD30+ lymphocytes. Hemorrhage, extensive necrosis and ulceration.	• Extranodal NK/T-cell lymphoma, nasal type • Cutaneous gamma/delta lymphoma • Anaplastic large-cell lymphoma (angioinvasive form)	• Association with EBV, mostly secondary cutaneous involvement (staging) • IHC: Expression of TCR gamma/delta, absence of expression of TCR alpha/beta • Clinical presentation with solitary or grouped nodules in pcALCL; staging examinations in sALCL.

Abbreviations: EBV, Epstein Barr virus; HTLV-1/2, human T-lymphotropic virus type 1/2; IHC, immunohistochemistry; LyP, lymphomatoid papulosis; MF, mycosis fungoides; NK, natural killer; pcALCL, primary cutaneous anaplastic large-cell lymphoma; sALCL, systemic anaplastic large-cell lymphoma; TCL, T-cell lymphoma; TCR, T-cell receptor..

cal cytomorphology of the tumor cells contrast with the favorable prognosis of PCALCL. (Table 2)

Clinical features

PCALCL manifests in most patients with a rapidly growing solitary tumor or grouped nodules with a tendency to ulcerate (Figure 2A). This lymphoma mainly affects people in their 6th decade with a male preponderance, but can also arise in childhood.[4] PCALCL has been described in human immunodeficiency virus (HIV)-infected individuals and organ transplant recipients.[29] The head and neck area as well as the extremities are the predilection sites.[30] Approximately 20% of the patients show multifocal lesions at different anatomic sites.[4,21] Remarkably, spontaneous tumor regression was reported to occur in 10% to 42% of PCALCL.[4,5] Recurrences after spontaneous regression, however, are common, and complete remission without therapeutic intervention is the exception.

Histopathological features

PCALCL manifests with a circumscribed nodular cohesive infiltrate of large lymphoid cells extending into the deep dermis or subcutis (Figure 2B). The tumor cells exhibit a pleomorphic, anaplastic, or an immunoblastic morphology with round, irregularly shaped nuclei and abundant pale cytoplasm (Figure 2C). In most cases, only a few reactive cells such as neutrophils or eosinophils are present. Epidermotropism is usually absent or only subtle. Neutrophil-rich and eosinophil-rich PCALCL appear to be more common in immunodeficient patients and may clinically and histologically be misinterpreted as pyoderma gangraenosum.[31,32] Other variants of PCALCL include angioinvasive, intravascular, and keratoacanthoma-like forms.

The tumor cells in PCALCL carry an activated T-cell phenotype and express CD2, CD4 or CD8, and CD45RO, whereas CD3 may be absent or only weakly expressed. By definition, CD30 has to be expressed by at least 75% of the tumor cells (Figure 2D). In contrast with systemic ALCL, PCALCL expresses cutaneous lymphocyte-associated antigen (CLA) but is almost always negative for anaplastic lymphoma kinase (ALK) and often negative for EMA. Clonal rearrangement of the TCR genes is detected in 90% of the cases.[33] The translocation t(2;5)(p23;q35) involving the *ALK*/nucleophosmin (*NPM*) genes, which is found in approximately 60% of systemic ALCL, is usually not present in PCALCL.[34] However, recently rare cases of ALK-positive PCALCL were described.[35] Rearrangements of the IRF4-DUSP22 locus on 6p25.3 were identified in 28% of PCALCL cases.[36]

Diagnosis

PCALCL is diagnosed and distinguished from other lymphomas by clinicopathologic correlation and staging. Radiologic staging

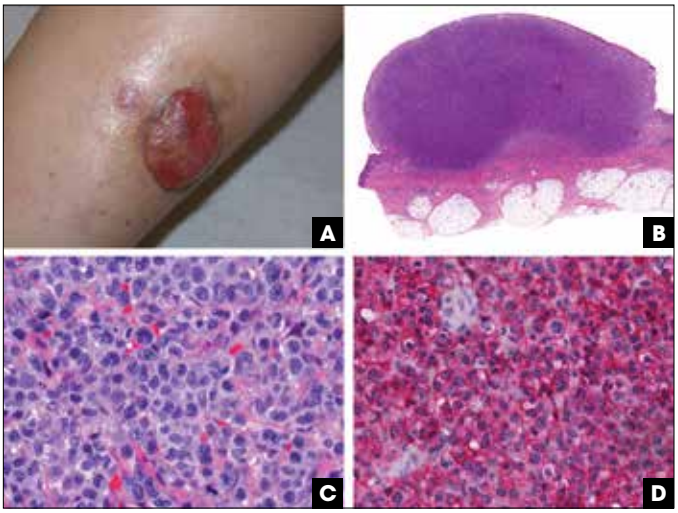

FIGURE 2. Primary cutaneous anaplastic large-cell lymphoma: **(A)** Ulcerated and fungating tumor on the right leg. **(B)** Polypoid lesion of dense tumoral infiltrate (H&E, magnification 2.5x). **(C)** Cohesive infiltrates of large pleomorphic and anaplastic lymphoid cells (H&E, magnification 200x). **(D)** Expression of CD30 by all tumor cells (immunohistochemistry, CD30 stain, magnification 200X). Abbreviation: H&E, hematoxylin–eosin.

examination (computed tomography or positron emission tomography/computed tomography) is essential for excluding secondary cutaneous infiltration by a systemic ALCL. Bone marrow biopsy is no longer considered to be mandatory, especially in patients with negative radiologic staging examinations.[5,37] Underlying immunodeficiency, particulary HIV infection, should be excluded.

Differential diagnosis of PCALCL includes a broad range of primary cutaneous and systemic large-cell lymphomas, including LYP (papulonodular lesions with regression) and MF tumor stage (preceding patches and plaques), which can both be distinguished by their different clinical presentation. Cutaneous peripheral T-cell lymphoma, unspecified or not otherwise specified, shares histological features with PCALCL, but CD30 is usually absent or expressed by a minority of the tumor cells.[38] Several other CTCL and to a much lesser extent cutaneous B-cell lymphomas can show expression of CD30 by the tumor cells.[39] In addition, expression of CD30 may also occur in histiocytic disorders, mastocytosis, as well as in angiosarcoma (for review see reference 40).

Prognosis

PCALCL carries a favorable prognosis with a 5-year survival rate over 90%.[4,41] However, PCALCL arising on the legs shows an impaired prognosis with a 5-year survival rate of 76%.[41] In addition, extensive limb involvement and progression to extracutaneous disease are independent adverse prognostic factors.[42] Involvement of locoregional lymph nodes alone, however, does not appear to be associated with a worse prognosis, but these data are based only on 1 study with a limited number of patients and need to be confirmed by larger studies.[4] Skin-limited relapses of PCALCL occur in 39% of patients and extracutaneous spread in 13% of the patients.[43] In contrast to immunocompetent individuals, immunosuppressed patients with PCALCL experience a more aggressive course and a worse prognosis.[44,45]

TABLE 2 Primary cutaneous anaplastic large-cell lymphoma: clinical, histopathological, and genetic features

Clinical criteria:
• Solitary, grouped or multifocal nodular lesions
• No clinical evidence of LyP, mycosis fungoides, or other type of cutaneous T-cell lymphomas.
Histological criteria:
• Nodular dermal infiltrate composed of large pleomorphic, anaplastic or immunoblastic cells.
Immunphenotypical criteria:
• Expression of CD30 by at least 75% of tumor cells.
• Expression of CD4 or CD8 in most cases with variable loss of pan-T-cell antigens (CD2, CD3, CD5).
• ALK-1 (p80) and t(2;5) translocation usually absent.
Staging:
• No evidence for extracutaneous lymphoma manifestation

Treatment

Surgical excision and radiotherapy are recommended first-line therapies for solitary or grouped PCALCL.[5] A dose of 20 Gy has been identified as an optimal dose for local radiotherapy of solitary or localized skin lesions and a dose of 8 Gy as sufficient for multifocal or relapsing PCALCL.[46] Multiagent chemotherapy is only indicated for extracutaneous tumor spread beyond locoregional lymph nodes. The best treatment for multifocal PCALCL and PCALCL in immunosuppressed patients needs still to be determined, but methotrexate is effective in some patients. Recent advances in the treatment of PCALCL were achieved by the introduction of BV as outlined below.

CD30 as therapeutic target

CD30 is an ideal antigen for targeted therapy due to its preferential expression on tumor cells and its limited expression on normal cells under physiological conditions. Binding of CD30L to its receptor on the $CD30^+$ tumor cells can result in apoptosis of cultured tumor cells.[3] BV is a CD30 antibody–drug conjugate composed of the cytotoxic antitubulin agent monomethyl auristatin E, which is covalently linked to a chimeric monoclonal anti-CD30 antibody. It has been approved for systemic ALCL and HL, as well as for patients with cutaneous anaplastic large-cell lymphoma and MF with CD30 expression, who have received prior systemic therapy. In a recent international, open-label, randomized phase 3 multicenter trial of BV (1.8 mg/kg once every 3 weeks; ALCANZA study) in primary cutaneous $CD30^+$ LPD, an objective global response was achieved in 56.3%.[47] Peripheral neuropathy, however, was observed in 67% of the patients, representing one of the major adverse effects of BV. Treatment with BV at lower doses and/or at longer intervals may decrease the risk for peripheral neuropathy without resulting in loss of therapeutic efficacy.[48] Remarkably, BV is not only effective in CD30 LPDs but also in other forms of CTCL with variable expression of CD30 such as MF, Sézary syndrome, and cutaneous gamma-delta T-cell lymphoma.[49,50] In those CTCL forms, response

to BV was observed even in patients with a low number of CD30+ tumor cells.[51]

Conclusion

Cutaneous CD30+ LPD span a spectrum of diseases with expression of CD30 by the neoplastic cells as the common denominator and favorable prognosis despite histological features suggesting a high-grade malignant lymphoma. Differences in their clinical presentation underline the crucial role of clinicopathological correlation in the diagnostic work-up. Recent advances in target therapy have led to new therapeutic approaches to CD30+ LPD. Therefore, assessment of CD30 in a variety of lymphomas as well as in an increasing number of other neoplasms has not only diagnostic and prognostic, but also important, therapeutic implications.

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