Primary cutaneous CD30+ T-cell lymphoproliferative disorders (CTCL) account for approximately 30% of primary cutaneous T-cell lymphomas (CTCL), thereby representing the second most common form of CTCL. 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 as the hallmark of these lymphomas.14,15 Additional rare and unusual histopathological 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 angioinvasive LYP type E, rapidly evolving, eschar-like necrotic lesions reaching a diameter of up to 4 cm may develop. Sometimes hypopigmented or hyperpigmented variciform 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 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.

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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 multianti-

Prognosis
LYP persists usually for several months or years, but is not associated with increased mortality per se.5,21 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.20 Remarkably, the rapid growth phase of tumor lesions and the highly atypi-

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

**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. PCALCL has been described in human immunodeficiency virus (HIV)-infected individuals and organ transplant recipients. The head and neck area as well as the extremities are the predilection sites. Approximately 20% of the patients show multifocal lesions at different anatomic sites. Remarkably, spontaneous tumor regression 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 (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. Other variants of PCALCL include angioinvasive, intravascular, and keratoacanthoma-like forms.

The tumor cells in PCALCL carry an activated T-cell phenotype and express CD8 and CD30. Atypical lymphocytes with expression of CD30...
Prognosis with a 5-year survival rate of 76%.41 In addition, extensive experience a more aggressive course and a worse prognosis.44,45

nocompetent individuals, immunosuppressed patients with PCALCL expression of CD30 by the tumor cells. 39 In addition, expression and to a much lesser extent cutaneous B-cell lymphomas can show expression of CD30 may also occur in histiocytic disorders, mastocytosis, as well as in angiosarcoma (for review see reference 40).

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.3 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

### Treatment

Surgical excision and radiotherapy are recommended first-line therapies for solitary or grouped PCALCL.3 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.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

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

<table>
<thead>
<tr>
<th>Clinical criteria:</th>
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<tbody>
<tr>
<td>• Solitary, grouped or multifocal nodular lesions</td>
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<tr>
<td>• No clinical evidence of LyP, mycosis fungoides, or other type of cutaneous T-cell lymphomas.</td>
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<table>
<thead>
<tr>
<th>Histological criteria:</th>
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<tr>
<td>• Nodular dermal infiltrate composed of large pleomorphic, anaplastic or immunoblastic cells.</td>
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</table>

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<tr>
<th>Immunohistotypical criteria:</th>
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<tr>
<td>• Expression of CD30 by at least 75% of tumor cells.</td>
</tr>
<tr>
<td>• Expression of CD4 or CD8 in most cases with variable loss of pan-T-cell antigens (CD2, CD3, CD5).</td>
</tr>
<tr>
<td>• ALK-1 (p80) and t(2;5) translocation usually absent.</td>
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<th>Staging:</th>
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<tr>
<td>• No evidence for extracutaneous lymphoma manifestation</td>
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**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.
to BV was observed even in patients with a low number of CD30+ tumor cells.\textsuperscript{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.

**References**


